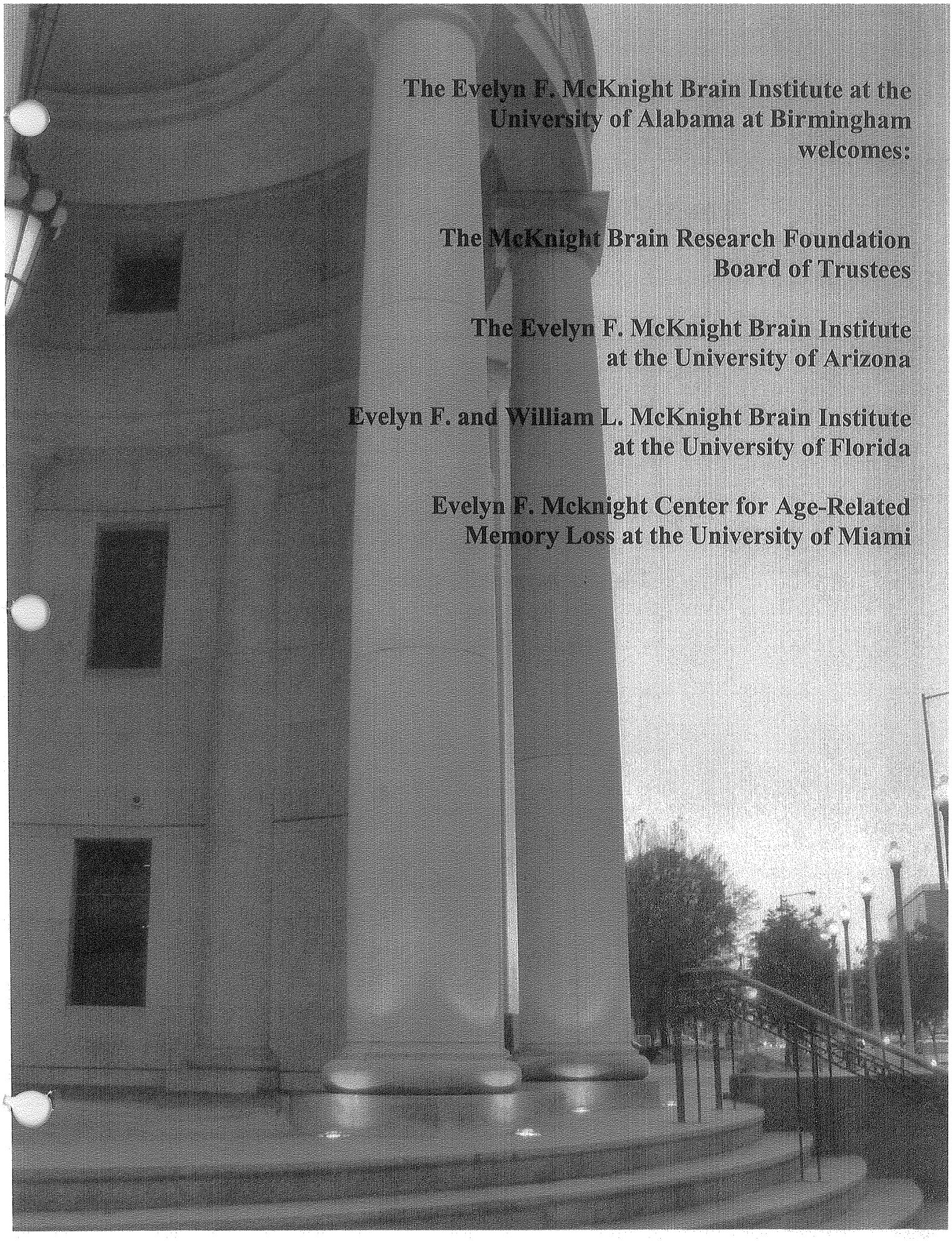

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Evelyn F. McKnight Brain Institute Meeting Participants
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Director, Evelyn F. McKnight Brain Institute
Evelyn F. McKnight Endowed Chair for
Learning and Memory in Aging

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Vice Chair, Department of Neurobiology
Associate Director, Evelyn F. McKnight
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Scientific Director, Alabama Neuroscience
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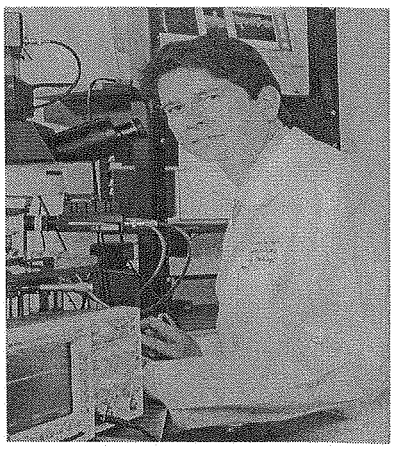

Dr. Sweatt's research program focuses on molecular mechanisms underlying learning and memory. Dr. Sweatt uses knockout and transgenic mice to investigate signal transduction mechanisms in the hippocampus, a brain region known to be critical for higher-order memory formation in animals and humans. His laboratory also uses a large number of genetically engineered mouse models for human learning and memory disorders in order to investigate the molecular and cellular basis of human memory dysfunction. His laboratory has discovered a number of new roles and mechanisms of gene regulation in memory formation, focusing on studies of transcription factors, regulators of chromatin structure, and other epigenetic mechanisms such as chemical modification of DNA. Overall his work seeks to understand the role of regulation of gene expression in synaptic plasticity and long-term memory formation and storage. His laboratory also is interested in using what they have learned about the molecular basis of hippocampal synaptic plasticity and memory formation to generate insights into human pathological conditions associated with aging-related memory dysfunction.

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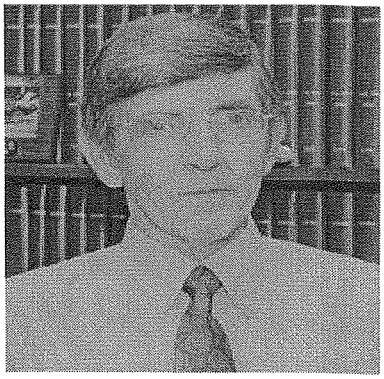

Dr. Hablitz's research is centered on understanding control of activity in local cortical circuits. He is using studies on synaptic transmission to further understand basic biophysical properties of mammalian central neurons, as well as to explore the pathophysiology of experimental epilepsy. Whole-cell voltage-clamp recordings from visually identified neurons are used in *in vitro* brain slice preparations. The goal of these studies is to determine the types of synaptic interactions present among pyramidal cells and interneurons in neocortex and how these patterns change over the lifespan. A particular goal is to understand how dopamine, an important modulator of working memory, affects excitability of individual neurons in prefrontal cortex. Additional studies involve the use of imaging techniques to directly visualize activity in presynaptic nerve terminals. These studies examine modulation of neurotransmitter release in normal neocortex and animal models of cortical dysplasia.

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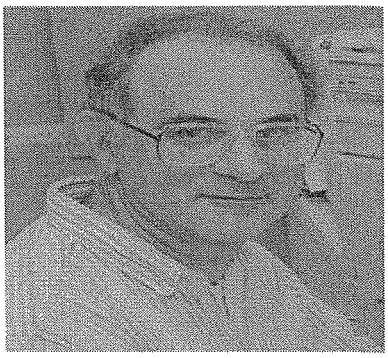

Dr. Brenner's laboratory studies the molecular biology of astrocytes, the most common cell type in the central nervous system (CNS). Astrocytes are responsible for many of the homeostatic controls in the CNS, such as maintaining the blood-brain barrier and proper neurotransmitter levels. Astrocyte serve as precursors for neurons and oligodendrocytes during development, and also serve as stem cells for the production of these cell types in the adult. CNS injury stimulates astrocytes to undergo a reactive response, which contributes to healing but can also lead to further damage. The work focuses on the transcriptional regulation of a gene encoding an intermediate filament protein specific to astrocytes, glial fibrillary acidic protein (GFAP), and on the biological role of this protein. The GFAP gene is of interest because it is turned on as astrocytes mature, and its activity increases dramatically during the reactive response. Thus, study of GFAP transcription will yield insights into mechanisms governing development, reaction to injury, and cell specificity, ultimately allowing these processes to be manipulated.

Dr. Brenner's laboratory has also discovered that heterozygous coding mutations in the GFAP gene are responsible for Alexander disease, a rare but fatal neurological disorder. Interestingly, although this establishes that the primary genetic defect in this disease is in astrocytes, the infantile form of Alexander disease is marked by massive myelination defects, and the later onset forms by neuronal dysfunction. Thus the study of this disorder not only has direct clinical implications, but also will reveal critical interactions between astrocytes and oligodendrocytes and between astrocytes and neurons that occur throughout the life span.

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As the Scientific Director of the Electrophysiology Neuroscience Blueprint Core Facility at UAB, Dr. Campbell examines electrophysiological phenotype of various genetically engineered mouse models in terms of cellular biophysics, baseline synaptic transmission and plasticity. The Core offers investigators at UAB and other institutions access to a state-of-the-art facility for mouse characterization. As a postdoctoral fellow in Dr. J. David Sweatt's laboratory, Dr. Campbells' research focuses on the effects of altering epigenetic mechanisms on synaptic transmission and ion channel activity. Her research involves the use of electrophysiological techniques utilizing *in vitro* brain slice preparations to ascertain how alterations in DNA methylation and histone acetylation affect the function of ion channels involved in long-term plasticity. Her broader questions are aimed at discerning if modifications in epigenetic mechanisms lead to changes in the expression or function of ion channels in neurodegenerative diseases.

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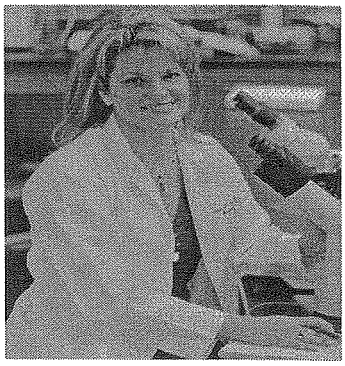

Dr. Gross' interest is in G protein-coupled receptor (GPCR) trafficking and signaling in neurons. One of the most fundamental problems in molecular neuroscience and cell biology is the proper assembly of signal-transducing membranes including the transport and sorting of protein components. A major cause of neurodegenerative and other inherited disorders is the improper localization of receptors and other signaling or transport proteins. The Gross Lab uses the dim-light photoreceptor protein rhodopsin as a model GPCR to better understand this process in the neural retina, and has been investigating the molecular interactions of proteins that interact with rhodopsin during folding, transport and those involved in the biogenesis of disk membranes in the outer segments of rods. In addition, using transgenic *X. laevis* and knock-in mice expressing mutants and fusion proteins of rhodopsin, they are studying both the molecular mechanisms of retinal degeneration as well as *in vivo* imaging of rhodopsin trafficking in live animals.

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The main goal of Dr. Kadish's research is to elucidate the role of white matter pathology in age-related cognitive deficits.

Her studies indicate that relatively early in the aging process changes occur in the crosstalk between astrocytes and oligodendrocytes that ultimately lead to malfunctioning of oligodendrocytes, and demyelination of axons. The studies also indicate that cholesterol metabolism is disturbed early in the aging process in the white matter, specifically in astrocytes, and since the astrocytes are the main source of cholesterol in the brain, and the main source of cholesterol for oligodendrocytes, this likely leads to changes in the myelin sheath. The lab investigates these changes in astrocyte functioning and communication in the white matter, and the development of cognitive impairments, using behavioral, immunohistochemical and molecular biology approaches.

A secondary research interest is the role of vascular (white matter) pathology in Alzheimer's disease. The relationship between small infarcts and cognitive decline is still not clearly defined. The lab has shown that small ischemic infarcts increase parenchymal Aß deposition and worsen cognitive outcome. Further, they have found that infarcts involving the white matter have a significantly worse outcome.

Part of the current studies includes the use of therapeutic agents that may be promising in the alleviation or delay of neural and cognitive changes that occur with age.

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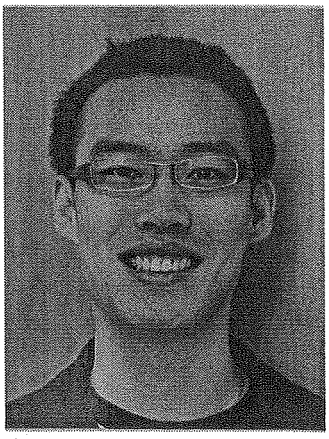

I am a graduate student in Dr. Parpura's lab. The main research interest of our laboratory is to understand the functional role of astrocytes in glial-neuronal interaction. Over the past decade, astrocytes are emerging as active participant in modulation of synaptic neurotransmission and it can achieve this by calcium-dependent exocytotic release of gliotransmitters such as glutamate, ATP, and D-serine. My specific project involved examination of agonist induced calcium oscillations and determinate how calcium oscillations control the release of gliotransmitters. The finding of this project will enhance our understanding of how information is transferred from neuron-to-astrocyte and vice versa.

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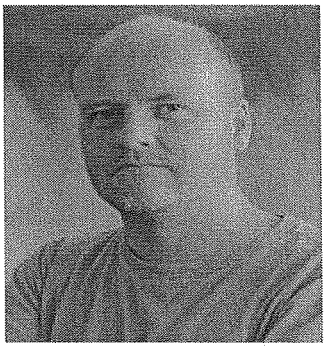

Dr. Lester's lab has been researching the role of CNS nicotinic acetylcholine receptors (nAChRs) in tobacco addiction and central synaptic transmission. nAChRs are ligand-gated ion channels composed of five individual protein subunits that cause neuronal excitation when bound and activated by synaptically released neurotransmitter, acetylcholine, or exogenous drugs like nicotine. In respect to drug addiction, they have been studying how exposure of these receptors to nicotine *in vivo* leads to persistent changes in hippocampal neuronal network activity following long-term withdrawal of the drug. In addition they have uncovered an unconventional form of diffuse synaptic signaling through nAChRs in the brain implying that this transmitter system may participate in volume transmission. Molecular biological studies have characterized at least ten receptor subunits that can be assembled together in numerous combinations giving rise to a wide variety of nAChRs with distinct functional roles. It is because of this diversity that nAChRs have been implicated in a range of CNS behaviors from pain sensation to learning and memory, and multiple pathological states such as aging, epilepsy and schizophrenia.

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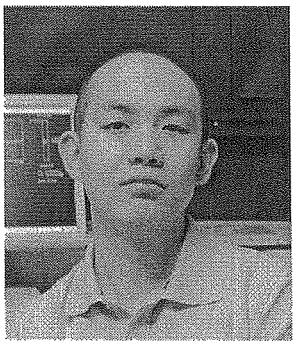

Dr. Liu's research is focusing on molecular mechanism of neurotransmitter release. Soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptors (SNARE) proteins Syntaxin, Synaptobrevin and SNAP25 are essential for exocytotic membrane fusion. Dr. Liu uses Atomic Force Microscopy (AFM) to study the intermolecular interactions between SNARE proteins at single molecule level. Mechanical properties and energetic information of SNARE complex are obtained, which provide insights of SNARE proteins and their functions in the mechanism of membrane fusion.

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Dr. Lubin's research is primarily directed towards characterizing the role of epigenetic mechanisms, such as histone modifications, DNA methylation, and signaling cascades that mediate the interaction of the NF-κB transcription factors to chromatin and determine how they participate in the regulation of gene expression as they relate to learning and memory and memory deficits associated with epilepsy. Her research program focuses on neurons and synapses in the hippocampus, an area of the brain that plays an important role in learning and memory. She is investigating the epigenetic regulation of brain derived neurotrophic factor (BDNF) transcripts during memory formation. This has lead to the discovery that exon-specific gene regulation of BDNF transcripts are dynamically regulated by DNA methylation and specific histone modifications in hippocampus during memory consolidation. Current work also includes an assessment of histone deacetylase (HDAC) inhibitors and demethylating agents that may be promising in the mitigation or disruption of cognitive disorders.

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My lab is currently investigating the role of estradiol in hippocampal synapse density, synaptic plasticity and learning. We are particularly interested in determining how loss of estradiol during aging impacts hippocampal function and whether hormone replacement therapy can activate estradiol-dependent mechanisms to restore normal synaptic function in hippocampus as well as hippocampal dependent learning and memory. Ovariectomized female rats treated with estradiol at various intervals following ovariectomy are used as a model system. Experiments involve electrophysiological measurements of NMDA currents, synaptic transmission, and long-term plasticity in acute brain slices. We have recently reported that estradiol increases NMDA transmission mediated by NR2B containing receptors and that is causally related to the heightened LTP induced by estradiol. Determining how estradiol and hormone replacement affects hippocampal function could lead to development of therapies to alleviate hormone-dependent memory loss in aging.

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As Scientific Director of the UAB Behavior Core, Dr. Miller provides expertise in the design, implementation and analysis of behavior experiments, with a primary focus on learning and memory and psychiatric disorders. The Behavior Core encourages investigators from UAB, as well as external collaborators across the country, to take advantage of the opportunity to investigate the behavioral effect of molecular and genetic models of cognitive disorders. As a postdoctoral fellow in Dr. Sweatt's laboratory, Dr. Miller is investigating the role of epigenetic mechanisms in the storage and persistence of memories. This line of research has wide-ranging implications, from normal memory formation and age-related cognitive decline to schizophrenia. Dr. Miller was recently awarded a Pathways to Independence grant to merge her graduate and postdoctoral training by investigating the epigenetic mechanisms of drug addiction. In addition, Dr. Miller collaborates with another UAB McKnight investigator, Dr. Gavin Rumbaugh, on a project in his laboratory aimed at understanding the molecular basis of the earliest stages of memory formation. One goal of this research is to develop therapeutic agents that will enhance the formation of new memories and the maintenance of old memories.

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Dr. Montana's interest, within Dr. Sontheimer's research group, which predominantly study astrocyte-derived tumors, is in understanding the role of kallikrein-kinin system on changes in intracellular calcium concentrations in glioma cells.

Gliomas posses the unique ability to expand within the brain by eliminating normal brain cells to vacate room for their own growth by releasing glutamate, and spread within the brain by active cell migration. One of their preferred pathways of spreading is along the blood vessels. This intimate relationship of glioma cells with perivasculature assures necessary supplies of oxygen and nutrients essential for glioma growth, but also expose them to variety of factors, such are growth factors, chemokines, cytokines or kinins. Endothelial cells can initiate activation of the kallikrein-kinin system that triggers the release of bradykinin (BK). Immediate action of BK on glioma cells is elevation of cytosolic calcium concentrations, while long-term superfusion with bradykinin causes oscillations of intracellular Ca^{2+}.

More than 50% of glutamate release is in exchange for cystine being imported via system Xc, a cystine glutamate exchanger. However, significant amount of glutamate is released through different mechanisms. Dr. Montana's studies focus on release of glutamate through Ca^{2+}-depedent exocytosis. Glioma cells respond to extracellular ligands, e. g. bradykinin which cause an elevation of cytosolic Ca^{2+}. This increase in Ca^{2+} in turn recruits glutamate containing vesicles to the cell surface where they fuse and release glutamate into the peritumoral space. Furthermore, glioma cells show oscillatory changes in intracellular Ca^{2+} as they migrate. Dr. Montana studies prolonged exposure to low concentrations of bradykinin on glioma cells' migration and secretion of matrix metalloproteinases.

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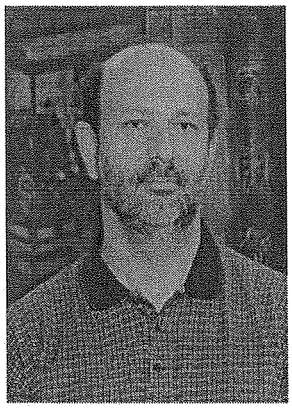

Glial cells were long considered to serve merely as the supporting cast and scenery against which the starring neuronal roles would be played out. Relatively recent evidence, however, indicates that glial cells are intimately involved in many of the brain's functions, including its computational power. Our research has been instrumental in demonstrating a novel functional role for glial cells. Hence, astrocytes, a sub-type of glial cell, can exocytotically release the neurotransmitter glutamate and, in turn, that glutamate released from astrocytes can signal to adjacent neurons. Indeed, by releasing glutamate, astrocytes can modulate synaptic transmission in response to experimental stimuli. Since intracellular calcium ion levels critical for secretion from astrocytes are within the physiological range, this release of glutamate from astrocytes could represent an additional site for modulation of synaptic transmission and integration in the CNS. Some current work also employs atomic force microscopy (AFM) in examining the interactions between pairs of molecules such as syntaxin and synaptobrevin that reside in astrocytes (and within synaptic junctions) and that are critical for glutamate release.

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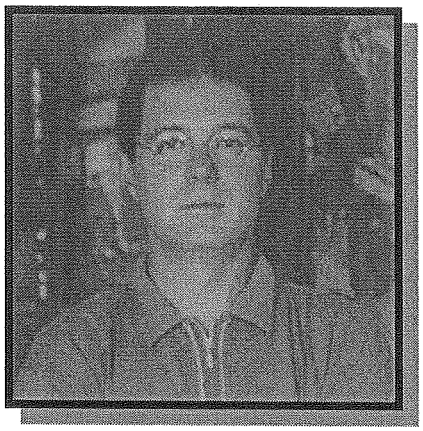

The long-term research interest of the Pozzo-Miller lab is to characterize the functional role of structurally defined neuronal compartments such as dendritic spines, dendrites and presynaptic terminals, and how they participate in synaptic development, function and plasticity as they relate to learning & memory and neurodevelopmental disorders. We specifically focus on the actions of neurotrophins in the hippocampus. Neurotrophins such as brain-derived neurotrophic factor (BDNF) are secretory proteins that regulate neuronal survival and differentiation, as well as synapse development, function and plasticity. Neurotrophic factors are strong candidates to provide the molecular signaling pathways mediating complex interactions leading to appropriate dendritic maturation and synapse development. We are currently investigating the "BDNF hypothesis" of Rett syndrome, a neurodevelopmental disorder of genetic origin associated with autism and mental retardation. Rett syndrome is associated with mutations in *MECP2*, a methylated DNA-binding transcriptional regulator of several genes, including *BDNF*. Tools: acute and cultured brain slices, neuronal cell cultures, transgenic mice, post-mortem brain samples, cDNA plasmids, sh/siRNA. Techniques: intracellular recordings, intracellular Ca^{2+} imaging, voltage-dye imaging, synaptic vesicle recycling, immunocytochemistry, electron microscopy, confocal microscopy, multiphoton excitation microscopy, diolistic cell labeling, quantitative analyses of neuronal and synaptic morphology, particle-mediated gene transfer.

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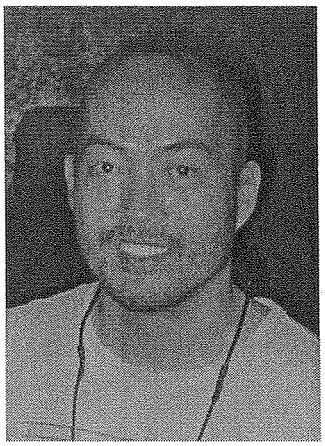

Reno is a student in Dr. Vladimir Parpura's lab and studies the regulators of intracellular Ca^{2+} in astrocytes, a cell type that has been shown to communicate with neurons bidirectionally. One way astrocytes converse back to neurons is through the release of the transmitter glutamate via vesicle fusion with the plasma membrane, a process regulated by intracellular Ca^{2+} levels. We have shown that mitochondria buffer transient increase in intracellular Ca^{2+} released from the endoplasmic reticulum, the primary Ca^{2+} store in astrocytes, thereby modulating the release of glutamate. While this finding is important in light of new insights relating astrocytic Ca^{2+} excitability to various age-associated neurological diseases, much is unknown how astrocytic mitochondrial energetics, and Ca^{2+} buffering and modulation of transmitter release affect cognition in the aging human brain.

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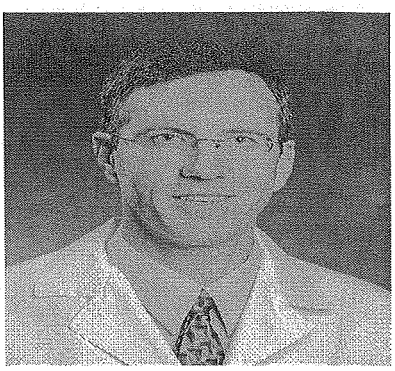

Dr. Roberson's laboratory is devoted to understanding the neurobiology of neurodegenerative diseases and thereby contributing to the development of better treatments for patients with these disorders. The lab is focused on two conditions, Alzheimer's disease and frontotemporal dementia, and largely on the role of the microtubule-associated protein tau. Tau is the major component of the neurofibrillary tangles in Alzheimer's disease, and mutations in tau cause frontotemporal dementia. The lab uses mouse models of these disease to study how tau contributes to neuronal dysfunction. In Alzheimer's models, Dr. Roberson has found that reducing the expression of tau makes the brain resistant to abeta, the peptide that drives neuronal dysfunction in AD. The lab is currently working on how tau reduction acts to prevent abeta-induced neuronal dysfunction. The group is also working on mouse models of frontotemporal dementia, and how tau mutations cause the abnormalities in social function, emotion, and neuropsychiatric symptoms seen in this disease.

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Dr. Roth's research focuses on applying integrative methods to examine many aspects of spatial ecology. He uses molecular, neurophysiological, behavioral, and ecological techniques to address questions related to spatial environmental interactions, animal navigation, and spatial learning and memory. Currently he is examining the role of molecular epigenetic mechanisms in maintaining spatial representations of the environment within the hippocampus.

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The goal of Dr. Roth's research is to determine how early social experiences influence the developing brain. She is particularly interested in the lasting effects of early-life adversity on molecular mechanisms of synaptic plasticity, and whether this contributes to deficits in cognition and emotion across the lifespan. Her current research efforts utilize a rodent model of caregiver maltreatment to understand the relationship between early-life adversity and the dysregulation of epigenetic molecular mechanisms underlying gene expression and memory formation. Behavioral and biochemical approaches are used in infant, adolescent, and adult animals to address this relationship.

Gavin Rumbaugh, Ph.D.
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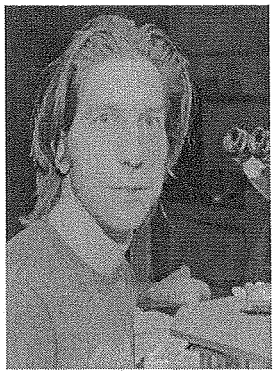

Dr. Rumbaugh's lab focuses on signaling pathways that are triggered by activation of NMDA receptors following vesicular release of glutamate from synaptic terminals. Activation of these receptors is critical for long-term changes in synaptic strength, which is believed to be one of many neural mechanisms that contribute to learning and memory in animals. Many of these signaling pathways (an example would be Ras/ERK activation) can regulate trafficking of AMPA receptors (AMPARs) to and from the synapse. Because AMPAR trafficking underlies certain forms of long-term synaptic plasticity, understanding the signaling pathways that regulate this trafficking will likely uncover mechanisms utilized during acquisition, consolidation and retrieval of memories. In addition, emerging evidence from several lines of research suggests that many common neurological disorders including Alzheimer's, schizophrenia and familial mental retardation are associated with synaptic dysfunction. Therefore, understanding signaling mechanisms that subserve synaptic plasticity and learning may help unravel the pathophysiology of common brain afflictions.

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Glial cells constitute over 50% of brain cells, yet their involvement in normal brain function is not fully understood. Unlike neurons, glial cells can migrate and divide in the adult brain and might act as stem cells, allowing repair of the brain after injury and disease. Uncontrolled proliferation of glial cells causes gliomas, the most deadly form of cancer. These tumors show invasive migration into normal brain, which impedes successful therapy. The transition between stem cells, normal glia and gliomas is poorly understood, as are biological adaptations that allow these cells to migrate and navigate through compact tissues. The broad goal of our laboratory is to understand how glial cells contribute to neuronal function in the healthy and diseased brain. We are currently studying mechanisms that allow glial cell migration during development, after injury and in malignancy. We are particularly interested in intrinsic adaptation that facilitate cell shape changes during migration and in the signals by which cells communicate with the normal brain environment. We are seeking to determine whether malignant transformation or acute injury induces novel invasion mechanisms or whether cells invoke the same machinery used for cell migration during brain development. We recently discovered that the secretion of Cl- through ion channels is an essential component for the invasion of glioma cells and a pharmacological Cl- channel inhibitor is currently being evaluated clinically. We are using a variety of techniques ranging from molecular biology, confocal and fluorescent cell imaging techniques to patch-clamp electrophysiology and a variety of cell migration/invasion models. We are routinely comparing properties of normal glial cells to glial cells associated with nervous system diseases. These studies employ primary cells and tissues derived from biopsies of patients presenting with glial tumors or other nervous system diseases.

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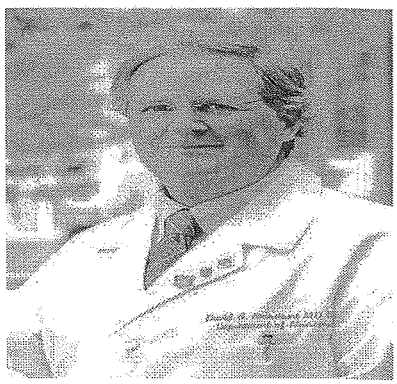

Dr. Standaert's laboratory is working on understanding both the root causes of Parkinson disease (PD) as well as the origin of the disabling symptoms that appear after long term treatment of the disease. The lab has a strong translational orientation – our goal is to accelerate the delivery of new therapies for Parkinson disease to the patients who desperately need them.

A primary focus of the laboratory is understanding the role of the protein alpha-synuclein in PD pathophysiology, and searching for novel approaches for protecting the brain from the effects of excess alpha-synuclein. We use a variety of cellular and rodent models, and are exploring the effects of several chaperone molecules, including those derived from open-ended screens in simple non-mammalian systems.

A related interest is the role of neuro-inflammation in PD. In human PD, there is a marked brain inflammatory response. Recent work in the Standaert lab using mouse models has led to the idea that this inflammation may be triggered directly by the presence of excess alpha-synuclein. The response involves both microglia as well as the adaptive immune system, and both components may be targets of therapies to prevent or retard the disease.

We are also exploring the effect of levodopa on brain function in PD. Levodopa remains the most effective existing treatment, but long-term therapy leads to many unwanted side effects ("wearing off" and "dyskinesia"). The Standaert lab has shown that many of the effects result from abnormal synaptic plasticity in the basal ganglia, and mislocalization of glutamate receptor systems. Recently, we found that the mechanisms responsible for the maintenance of this aberrant plasticity is likely the result of levodopa-induced epigenetic modifications.

Dr. Standaert directs the UAB Center for Neurodegeneration and Experimental Therapeutics (www.uab.edu/CNET) , which supports a broad program of laboratory and clinical studies aimed at developing better treatments for PD as well as other neurodegenerative diseases.

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Randy Stout is a graduate student in the neurobiology program and a member of the lab led by Dr. Vlad Parpura. The research conducted in the Parpura lab is focused on several different levels of nervous system function and Randy's main area of research is on how the activities that glial cells perform as a major component of the brain affect communication between each other and between neurons. Randy has developed tools to study glia in the model organism *C. elegans* to gain insight about how glial cells support synaptic transmission and behaviors such as movement and learning. This small worm has been used extensively by other researchers to study a wide range of neurobiological phenomenon from synaptic transmission to neurodegeneration. In contrast to humans and mice, *C. elegans* survive and respond to changes in their environment without any intact glial cells. Randy's research is aimed at capitalizing on this and many other advantageous attributes of *C. elegans* as a model organism to further scientific knowledge about the role that glial cells play in brain function under normal and disease conditions.

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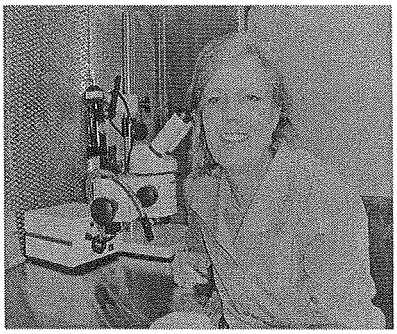

Many diseases are linked to dysregulation of second messenger signaling cascades. One important second messenger system is the phosphoinositide (PI) system, in which inositol lipids function as second messengers and cofactors for many cellular activities stimulated by growth and trophic factors, hormones, cytokines, and neurotransmitters. Dr. Theibert's research focuses on investigating the intracellular targets for several of the PI second messengers in the nervous system. They are particularly interested in the function of PtdInsP3 in neurons and glia, since they have demonstrated that this lipid is required for cells to extend processes, termed neurites, in response to trophic factors and extracellular matrix. Neurites eventually form mature axons and dendrites, which contact each other at synapses, and allow for information transfer between neurons. Using biochemical and molecular techniques, they have isolated and cloned several novel phosphoinositide receptors from brain. One of these receptors is involved in regulating vesicle trafficking and the actin cytoskeleton, two activities which are involved in neurite outgrowth and new synapse formation. Studies are underway to determine the role of these receptors in neuronal development and synapse formation, and the molecular mechanisms which regulate receptor expression, targeting to intracellular compartments, and modulation of activity. Several potential homologues of these receptors are present in the genetically tractable organism, Saccharomyces cerevisiae, which allows us to use yeast genetics to complement the biochemical and molecular approaches in dissecting the function of these brain phosphoinositide receptors.

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Research Interests

Amyloid angiopathy in cognitive dysfunction and Alzheimer's disease
In addition to the well-known accumulation of amyloid beta (Aβ) in neuropil plaques and intracellular sites, Alzheimer's disease (AD) is associated with substantial Aβ deposition in the cerebral vasculature. Whereas, clearly, cerebrovasc ular disease is not the sole cause of AD, mounting evidence indicates that cerebrovascular amyloid angiopathy (CAA) contributes to some aspects of the cognitive impairments associated with AD. These findings have led to the hypothesis that CAA contributes to neuronal dysfunction and thus egrees of CAA), to test these working hypothesis. cognitive impairment, possibly through brain hypoperfusion. We are testing the prediction that 1) CAA precedes neuropil Aβ deposition and 2) compared to the course of Aβ deposition in neuropil, CAA is more closely linked in time to the onset of cognitive impairment. 3) We also are examining the hypothesis that Aβ deposition in blood vessels is associated with altered blood flow, oxidative stress and inflammation that in turn will lead to cognitive deficits and finally, 4) we will study whether pharmaceutical reduction of cerebrovascular inflammation significantly reduces the development of CAA and brain Aβ deposition and attenuates the development of cognitive dysfunction.

Hypertension in cognitive dysfunction and Alzheimer's disease
Hypertension is a risk factor for stroke, cardiovascular disorders, and vascular dementia, and the incidence of these diseases grows with increasing blood pressure. Recent studies have shown that hypertension is also a risk factor for AD). AD is associated with the accumulation of Aβ in plaques in the brain parenchyma but also with substantial amyloid β deposition in the cerebral vasculature.

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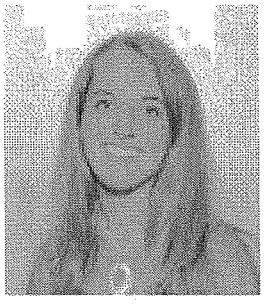

Lindsey Vedder's research interests are centered around the ability of 17β-estradiol (E2) to enhance synaptic plasticity and learning and memory. E2 increases long term potentiation (LTP) and NMDA receptor subunit 2B current in ovariectomized (OVX) rats up to 48 hours after E2 treatment. Under the mentorship of Dr. Lori McMahon, Lindsey aims to investigate the ability of E2 to enhance learning at varying intervals after E2 treatment in OVX rats to determine if the time course of E2 induced increase in learning is the same as the E2 induced increase in LTP. Lindsey will determine the role of the NR2B subunit in E2's ability to enhance learning and memory and also whether the mechanisms behind E2's effects on LTP and learning are maintained during aging in a rodent model of menopause. With a better understanding of how E2 can benefit cognitive function, more effective hormone replacement therapies could be produced for women with cognitive deficits due to menopause.

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Dr. Visscher is interested in characterizing what brain mechanisms underlie the human ability to flexibly process inputs from the environment. We often process the same information in different ways at different times. For example, sometimes we may hear a string of numbers (e.g. a phone number on a commercial from the radio) and try to remember it, while at another time, the same string of numbers may be irrelevant, and we may ignore it. Dr. Visscher uses a variety of tools to better characterize how human brain activity before a stimulus is presented may impact the ways in which that stimulus is processed. Behavioral measurements (psychophysics and eye movements), measurement of electrical activity in the human brain using EEG, and measurement of neural activity through fMRI allow a window into patterns of brain activity.

Dr. Visscher started at the University of Alabama at Birmingham in April 2009, after a postdoctoral fellowships at Harvard University, where she worked with Randy Buckner and studied how connectivity among brain areas (as measured with functional MRI) change with experience. She used psychophysical and EEG techniques to examine how brain activity before a stimulus influences whether a stimulus will interfere with items in working memory during a previous postdoctoral fellowship at Brandeis University working along with Robert Sekuler. She received her Ph.D. in Neuroscience from Washington University in St. Louis in 2004, where, with Steve Petersen she studied how techniques of fMRI can be used to examine different timecourses of neural activity.

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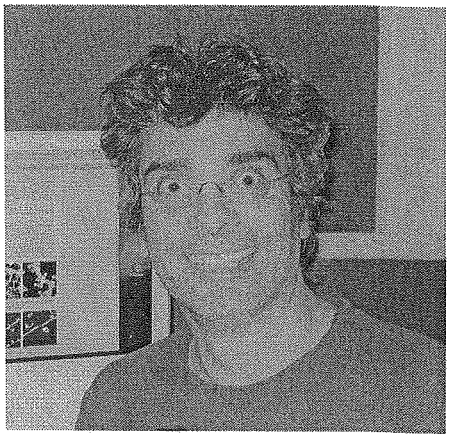

The balance of neurotransmitter release and reuptake dictates how information transfer occurs at specialized connections called synapses. At the majority of excitatory synapses in the CNS, action potential invasion leads to the fusion of glutamate-filled vesicles. Following release, glutamate acts at receptors and is ultimately taken up into neurons and glia by transporters.

The work in Jacques Wadiche's lab is geared towards understanding the beginning and end of glutamate's lifecycle as a neurotransmitter. To this end, work in the lab has uncovered how the precise timing of transmitter release is controlled by activity and its influence on the information transfer through the synapse. Wadiche and his colleagues have also determined that although the majority of glutamate is taken up into astrocytes, neuronal glutamate transporters are poised to regulate the activation of the more abundant perisynaptically-located receptors.

These studies will lead to a better understanding of the foundations for all thought, movement, and behavior: the milliseconds before, during, and following neurotransmitter release.

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The research in the laboratory of Dr. Linda Overstreet-Wadiche is focused on understanding the role of adult generated neurons in a region of the brain that is associated with learning and memory. Most neurons are generated during embryogenesis, but in the hippocampus newborn neurons are continuously produced throughout adulthood and growing evidence suggests that they participate in hippocampal-dependent cognitive and emotive functions. The proliferation, survival and integration of newborn neurons are regulated by many factors including aging and environmental enrichment, allowing adult neurogenesis to provide a link between experience and structural plasticity of the brain. Dr. Overstreet-Wadiche's lab uses transgenic mouse models and electrophysiological techniques to explore how experience-dependent factors control adult neurogenesis and how newborn neurons in turn participate in hippocampal network activity.

Scott Wilson, Ph.D.
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The focus of Scott Wilson's research is to investigate how regulated protein turnover by the ubiquitin proteasome pathway controls nervous system development and function. By using a combination of genetics, biochemistry, electrophysiology and behavioral analyses, the Wilson laboratory has investigated ubiquitin-signaling events that are required for synapse maturation, the induction of synaptic plasticity, learning and memory in mice. Results from these studies demonstrate the importance of localized ubiquitin recycling to maintain efficient protein turnover at synapses and indicate that changes in ubiquitin homeostasis may contribute to neurodegenerative diseases.

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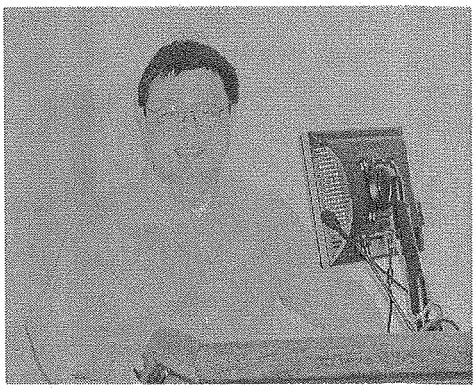

High resolution and high sensitivity molecular imaging provides critical insights in understanding cellular and molecular interactions in living tissues. Imaging depth and molecular contrast are two essential problems that need to be solved in *in vivo* microscopy. Having worked in the field of ultrafast laser spectroscopy for many years, I am now focusing on developing imaging techniques that can provide increased imaging depth with abounding molecular contrasts in optical microscopy by taking advantage of achievements from nonlinear optics and laser spectroscopy. For example, one of our approaches is using near infrared ultrafast laser pulses to generate fluorescence of fluorophores through multiphoton excitation, which provides imaging depth up to 500 micron (in brain slices) with sub-micron resolution and additional benefits, such as high photo-bleach thresholds and confined photo-damages. The multiphoton fluorescence microscopy makes it possible for us to image mouse brains in vivo through thinned skulls or cranial windows. There are certainly a lot more nonlinear optical processes that can provide useful molecular contrasts in imaging; for example, second harmonic, third harmonic, coherent anti-Stocks Raman scattering and transient absorption have been explored in various cell and tissue imaging. Through the newly established Neuroimaging Core in the Alabama Neuroscience Blueprint Core Center, we will specifically address the microscopy imaging needs from the neuroscience research community by developing advanced microscopy techniques.

Evelyn F. McKnight Brain Institute Meeting Participants
University of Arizona

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Director, Evelyn F. McKnight Brain Institute
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The central goal of Dr. Barnes' research and teaching program is the question of how the brain changes during the aging process and the functional consequences of these changes on information processing and memory in the elderly. Her research program involves studies of behavior and neurophysiology in young and old laboratory animals. This work provides a basis for understanding the basic mechanisms of normal aging in the brain and sets a background against which it is possible to assess the effects of pathological changes such as Alzheimer's disease. Some current work also includes an assessment of therapeutic agents that may be promising in the alleviation or delay of neural and cognitive changes that occur with age. Dr. Barnes is a Regents' Professor at the University of Arizona, Director of the Evelyn F. McKnight Brain Institute at the University of Arizona and recipient of the Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging. The objective of the Evelyn F. McKnight Brain Institute is to uncover the neurobiological changes in the brain that cause memory changes as we age, and to unravel which changes are due to normal aging and which are due to disease states.

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Dr. Alexander's research and academic interests focus on the study of brain-behavior relationships in the context of aging and age-related, neurodegenerative disease. He uses neuroimaging techniques, including structural and functional magnetic resonance imaging (MRI) and positron emission tomography (PET), in combination with measures of cognition and behavior to address research questions on the effects of healthy aging and Alzheimer's disease on the brain. A major focus of his research program includes the use of univariate and multivariate network analysis techniques with multiple neuroimaging methods and measures of neuropsychological function, health status, and genetic risk to help elucidate the mechanisms of human cognitive aging and to advance understanding on how these multiple factors interact to influence cognitive function as we age. Dr. Alexander's research also includes the application of these techniques to non-human animal models of aging and age-related disease. He is Professor in the Clinical and Cognition & Neural Systems Programs and directs the Brain Imaging, Behavior & Aging Lab in the Department of Psychology. Dr. Alexander has a faculty appointment in the Evelyn F. McKnight Brain Institute and directs the MRI Morphology Core of the Arizona Alzheimer's Research Center.

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Kaitlin Bergfield's research focuses on the study of aging, age-related cognitive decline, and Alzheimer's disease, using univariate and multivariate network analysis techniques with structural MRI. Recently, Kaitlin's research showed a network pattern of gray matter volume reductions associated with healthy aging. This work suggests that the age-related network pattern was reproducible across multiple samples and supports the preferential involvement of frontal and selected temporal regions in healthy aging.

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The central goal of Sara Burke's post doctoral research is the question of how age-associated changes in attention may contribute to memory impairments in the elderly. Recently, Sara completed her dissertation entitled, "A perceptual-mnemonic role for the perirhinal cortex in age-associated cognitive decline". Her thesis work involved examining how functional changes in the aged perirhinal cortex contribute to the impairments in stimulus recognition that have been observed in aged animals.

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The primary goal of Dr. Chawla's research is the question of how the brain changes during the normal aging process and the functional consequences of these changes on information processing and memory in the elderly. Her research involves behavioral studies of immediate-early genes and neural plasticity mechanisms using spatial and temporal compartmental analysis in young and old laboratory animals. This work provides a basis for understanding the basic mechanisms of normal aging in the brain and sets a background against which it is possible to assess the effects of pathological changes such as Alzheimer's disease. Dr. Chawla is a Assistant Research Scientist and heads the molecular research team in Dr. Carol Barnes laboratory at the University of Arizona, Evelyn F. McKnight Brain Institute and the ARL Division of Neural Systems Memory and Aging at the University of Arizona.

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Emily Connally attempts to better define thresholds for detrimental age-related decline, specifically in examining neuropsychological assessment measures and their ability to predict everyday functioning in normal older adults. Emily is currently working on 3 projects, with a selection of diverse measurements, including surveys, standardized neuropsychological measures, experimental memory paradigms, functional neuroimaging, and virtual reality. Such a multifaceted approach is necessary because of the variance in performance across several cognitions in this special population.

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Alaina Glatting graduated last May with a BA in Psychology and a BS in Physiological Sciences from the University of Arizona. She is currently a first year Masters student in the Physiological Sciences Program and is working on writing her thesis in neuroscience. Alaina has previous experience with hippocampal single cell recordings and is interested in path integration and the processing of spatial information. Building on this background, Alaina is currently focusing on a behavioral and hippocampal ensemble recording study in young and aged rats, using the spatial eyeblink conditioning task that Dr. Leslie Schimanski has developed to examine possible age differences in spatial memory accuracy. Ms. Glatting will be applying to medical school in the upcoming year, and feels that it is important to gain a foundation in and exposure to research before going on to her clinical studies.

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Elizabeth Glisky's research interests include changes in memory and executive function that occur as a result of normal aging or age-related neurological conditions such as Alzheimer's disease. Recent collaborative work has focused on tracking longitudinal changes in cognitive function in a cohort of normally-aging older adults, and relating those changes to measures of brain integrity, genetic predisposition, and other health variables. The goals of this research are to understand the variability in the normal aging process, to identify early indicators of what might be abnormal aging, and to design and implement interventions that might be instrumental in enabling older adults to maintain optimal memory function into the oldest years. Dr. Glisky's work has been supported by the National Institute on Aging, the Arizona Biomedical Research Council, the Arizona Alzheimer's Consortium, and the Evelyn F. McKnight Brain Institute.

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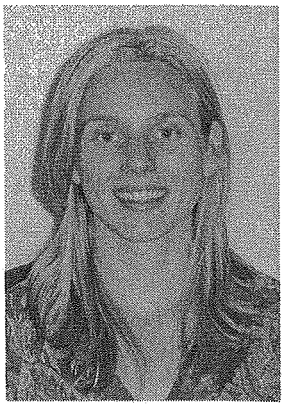

Krista Hanson's research focuses on investigating the differences between pathological and non-pathological aging, with an emphasis on Alzheimer's disease and pre-Alzheimer's cognitive declines. Her approach to investigating this problem primarily has involved multivariate statistical methods paired with voxel-based morphometry processing of structural MRI's correlated with behavioral measures of cognitive performance. Recently, Krista's research has shown a correlation between a network pattern of gray matter volume reductions associated with a continuum from healthy aging to amnestic mild cognitive impairment to Alzheimer's disease and attentional measures. Furthermore, expression of this network pattern of gray matter reductions was associated with conversion to Alzheimer's dementia in individuals with amnestic mild cognitive impairment.

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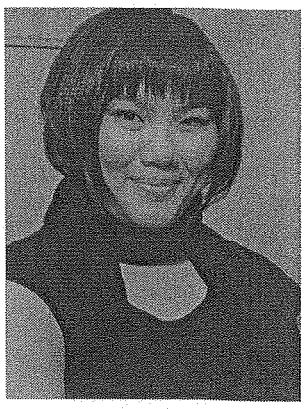

The central goal of Lan's research interests lie in investigating the plasticity of the nervous system. Specifically, Lan's doctoral thesis is aimed at exploring the neural correlates of reward by studying the characteristics of the dopaminergic neurons found in the ventral tegmental area and how these may change during normal aging. High density neural recording ensembles as well as molecular imaging techniques are being utilized to achieve a greater understanding of not only the systems level response to reward, but also to gain insights into the possible processes that underlie age-related cognitive decline.

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The seeds of my curiosity in neural systems were planted by an enquiry regarding the paradox of stereotaxic surgery in the treatment of neurological disorders. How could dysfunctional neural circuits benefit from the removal of otherwise necessary brain structures? The efficacy of such treatments contradicts current understanding of neural networks. In aging, the subtlety of the neuronal changes and the significant impact they have on cognitive function make the desire to understand neural circuits even more intriguing. The inevitability of aging brings urgency to our quest to understand age-related changes in the neural circuitry and the need to develop strategies towards healthy cognitive aging.

The hippocampal formation is involved in the acquisition and processing of information about the relationship between stimuli and events to form episodic memories. Within the hippocampal formation, the fascia dentata (dentate gyrus) is the region most vulnerable to age-related changes. Synaptic connectivity is compromised through the pruning of the entorhinal cortex, reduction of NMDA receptors and the loss of synapses. In addition, there is a reduction in the cerebral blood flow and in the expression of the behavior induced immediate early gene, *Arc*. Despite the apparent vulnerability of the fascia dentata during aging, surprisingly little is understood about how the firing activity of its principal neurons, the granule cells, is altered during behavior in aged animals. The main objective of my Ph.D. work under the supervision of Dr. Carol Barnes, is to make an age comparison of granule cell representations of an environment, and to study the consequence of perturbations of a familiar environment on granule cell ensembles. This study contributes to understanding how hippocampal networks that are involved in spatial memory are altered during normal aging processes.

Prior to my arrival to the University of Arizona for my Ph.D. studies in neuroscience, I completed my B.Sc. (Honors) degree at the University of Leicester (UK) and my M.Sc.(Med) degree at the University of Cape Town (South Africa). I have received the honor to be one of two women to be the first to be awarded the Levi-Montalcini Fellowship in Neuroscience for African Women from the Fondazione Rita Levi-Montalcini and the International Brain Research Organization.

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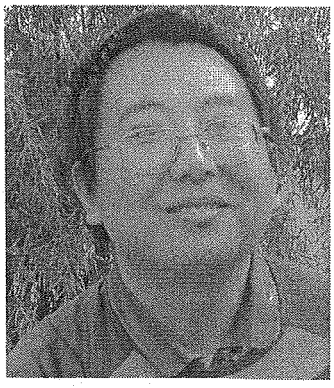

Dr. Lin received his Ph.D degree in Bioengineering at Arizona State University. His current research focuses on animal models of aging and Alzheimer's disease, translating human image analysis and acquisition methods for application to small animal and non-human primate studies, and applying new image analysis technique to human aging studies. He is now working on constructing MRI templates and atlas for neuroimaging studies of the mouse brain and developing an automated procedure to coregister histology images to 3D MRI volume.

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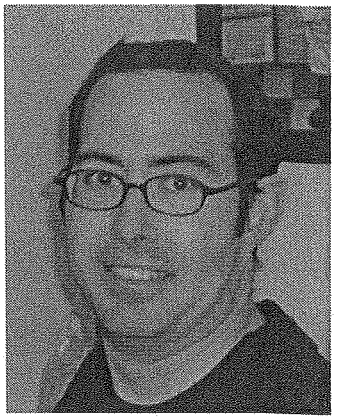

Dr. Lister received his doctoral training at Boston University researching the effects of prenatal protein malnutrition on the neuroanatomy of the adult rat hippocampal formation. After studying structure throughout graduate school, he came to NSMA to learn more about function, and is involved in efforts for automating whole brain imaging as well as projects that use the expression of immediate early genes (such as Arc and Homer) to map behavior-induced neural circuits. Current progress on automated brain imaging has focused on work with collaborators at Rensselaer Polytechnic Institute to automate montaging of high resolution confocal images encompassing entire cortical regions. He is also involved in using 3D catFISH to analyze encoding in the hippocampus and cerebral cortex in young and old animals to assess age-related impairments in the ability of these structures to represent information. 3D catFISH is a technique that combines fluorescent in situ hybridization with high resolution confocal microscopy of immediate-early gene expression to evaluate the exact neural circuits activated by behavior. Behaviorally relevant neuronal activity is known to induce the expression of certain immediate early genes, such as Arc. The localization of Arc mRNA within cellular compartments (nucleus vs. cytoplasm) is consistently time-dependent, allowing the researcher to probe multiple time points within the same animal. Current projects examine the effects of exercise on Arc expression and age-related differences in Arc expression in the hippocampus and entorhinal cortices during behavior.

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As a graduate student, Drew focused on short time-scale neuronal dynamics in CA1 of the hippocampus during linear track running. He has made a number of important discoveries in his dissertation, and his most recent work has provided the first direct evidence that, as an animal's velocity increases, there is 'sequence compression' of hippocampal cell firing within an individual cell's preferred firing location, suggesting the importance of temporal as well as spatial information in the activity of hippocampal ensembles. Dr. Maurer has recently joined the Barnes laboratory, where the focus of his research will be to investigate the neuronal activity within the primate medial temporal lobe in naturalistic conditions such as random foraging and sleep. This goal will be accomplished through the development of multi-unit, telemetric recording technology.

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In general, my primary research interest is directed at understanding how the brain changes during the normal aging process and how these changes may contribute to impaired memory function. Recent work has been directed at the question of whether age-associated changes in immediate-early gene transcription within the aged hippocampus is regulated by epigenetic mechanisms, such as DNA methylation.

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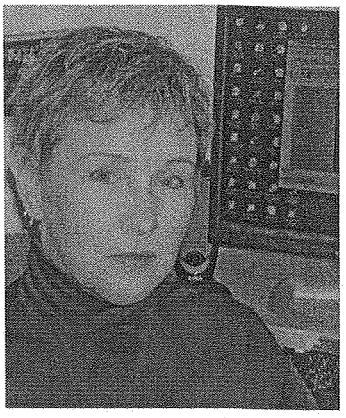

Dr. Lee Ryan received a Ph.D. in Cognitive and Clinical Psychology at the University of British Columbia in 1992. She is currently a faculty member of the Evelyn F. McKnight Brain Institute at the University of Arizona as well as the Director of the Cognition and Neuroimaging Laboratories, making magnetic resonance imaging (MRI) technology available to cognitive neuroscience researchers on campus. Her research focuses on the neural basis of memory and understanding how age-related changes in brain function affect memory in older adults. She has a special interest in memory disorders such as Alzheimer's Disease, and is currently conducting research using various MRI methods as a tool for detecting subtle markers of change in brains of individuals with risk for Alzheimer's disease prior to the onset of memory impairments.

As an associate professor in the Cognition and Neural Systems program and the Clinical Neuropsychology program at the University of Arizona's Department of Psychology, Dr. Ryan teaches undergraduate classes in human memory and graduate level courses such as Human Brain Behavior Relationships, Cognitive Neuroscience, and Principles of Neuroanatomy. As a clinical psychologist, Dr. Ryan works with individuals and families who are coping with chronic and progressive diseases that effect cognitive functioning, including multiple sclerosis, Parkinson's disease, and Alzheimer's disease.

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Dr. Samson's research examines the effects of normal aging on network activity underlying emotional learning, with particular attention aimed at age-related modifications of amygdala physiology and function. Older adults use different affective-cognitive strategies and show greater memory for positive stimuli compared to younger adults. Her project mainly involves assessing the behavioral performance of young and aged rats during an instrumental task in which the incentive value of the reward or the action-outcome contingencies are modified. The neuronal activity is also measured using multiple single cell recordings *in vivo* and correlated with the age-related changes in behavior. By comparing results from young adult and old rats, her work will provide insight into the mechanisms of age-related changes in emotional perception and processing. This will help distinguish between the normal aging process and pathological changes in cognitive function associated with AD.

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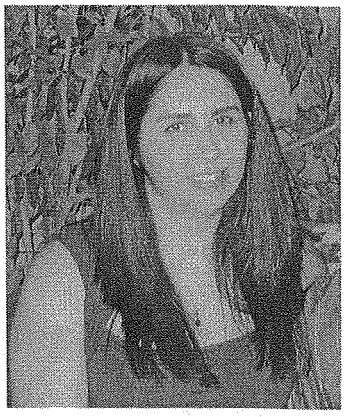

Dr. Schimanski's research focuses on age-related changes in hippocampal neurophysiology and spatial memory. She is examining whether there are differences in the way that young and aged rats learn locations of salient cues in an environment in a spatial version of a classical eyeblink conditioning task. Her project will determine how age-related changes of "place cell" properties in hippocampal area CA1 affect spatial memory. This work will shed light on the link between encoding of spatial information by hippocampal cells and use of this information by aged animals in a behavioral task. Dr. Schimanski was trained as an electrophysiologist and behavioral neuroscientist, and is currently a Post-Doctoral Associate at the University of Arizona and the Evelyn F. McKnight Brain Institute.

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Mr. Thome's research focuses on studying populations of neurons in the temporal lobe of awake and freely behaving primates using molecular imaging techniques as well as multiple single unit recordings. He is using freely navigating primates in real and virtual environments in combination with molecular imaging techniques. In particular, he is seeking to understand whether ensembles of neurons in navigation related structures show patterns of activation similar to those seen in rodents. In addition, the project aims to understand whether there exist differences in patterns of ensemble activity between real and virtual environments. This work will clarify basic questions regarding primate temporal lobe function and provide insight into the extensibility of findings in rodents to higher primates. A second set of experiments, using data from young and old primates, is aimed at understanding the functional role of oscillations in the primate temporal lobe and whether these change with age. Mr. Thome received an interdisciplinary B.A in Cognitive Science at the University of Arizona.

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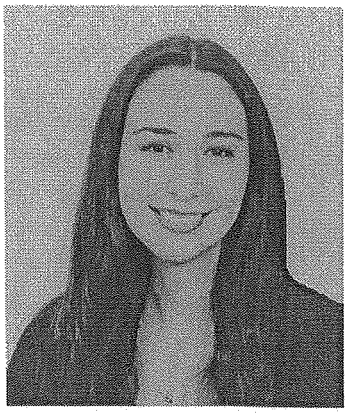

Michelle Valfre's research interests focus on relationships between individual differences in cognitive function, biomarkers, genetic risk factors, and neuroanatomical changes in both successful and pathological aging as measured by structural MRI. She is particularly interested in the application of multivariate network analysis techniques to investigate patterns of age-related gray matter atrophy. Future research aims to examine correlates of the functional neural networks underlying executive function and memory performance in cognitively normal older adults and risk factors for Alzheimer's disease.

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Katrin Walther is a postdoctoral fellow in the Cognition & Neuroimaging Laboratories. She is working on a project assessing the utility of diffusion-weighted magnetic resonance imaging (DWMRI) in identifying early neuropathological markers of Alzheimer's disease (AD) in healthy older adults with increased risk for AD, which might enable early diagnosis and early treatment. She earned her Ph.D. in Psychology at the University of Leipzig in Germany where her research was focused on the development of assessment and intervention methods for individuals with neurological impairment.

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Janelle Wohltmann is interested in characterizing functional differences among healthy aging adults in order to design novel techniques for the rehabilitation of cognitive deficits that occur in this population. Currently, she is examining differences in how older adults approach executive functioning tasks by using qualitative scoring of neuropsychological tests in order to examine things like organizational strategy. She is also interested in lifespan cognitive development, including the relationship between executive function development in children and executive function decline in older adults.

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Professor and McKnight Chair for Research on Aging & Memory

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Bruce Crosson, Ph.D.
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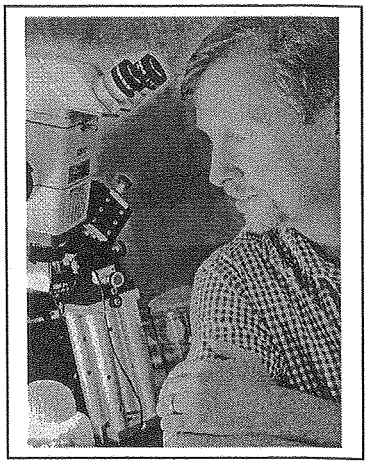

Summary of Current Research Interests

My research program utilizes a combination of behavioral characterization with biochemical, molecular, and electrophysiological techniques to obtain a vertically integrated perspective on neural aging, from the molecular to the cognitive level. The two main goals of the lab are to identifying mechanisms for age-related memory impairment and test treatments to alleviate memory deficits. Regulation of Ca^{2+} is thought to play a role in age-related neurodegeneration and the synaptic plasticity that underlies memory. Our research shows that rapid forgetting is associated with a shift in the threshold for Ca^{2+}-dependent synaptic plasticity, LTP and LTD. Subsequent research clarified the mechanisms and showed that age-related changes in synaptic plasticity are due to altered Ca^{2+} regulation involving NMDA receptors, voltage-dependent Ca^{2+} channels, and intracellular Ca^{2+} stores interacting with processes for cell excitability. Moreover, a shift in the activity of LTD/LTP signaling mechanisms (i.e. phosphatase/kinase activity) was found to underlie a decrease in synaptic strength and correlate with memory impairment. These signaling cascades impinge on transcriptional regulation and recent work has examined gene expression associated with memory decline during aging. Current research is addressing the undying cause of altered Ca^{2+} regulation and is focused on homeostatic processes of oxidative stress and protein degradation pathways. This body of work characterizes several biological markers of age-related memory impairment and provides a model linking age-related memory decline with major hypotheses for aging, altered Ca^{2+} homeostasis and oxidative stress, through a change in Ca^{2+} signaling cascades to markers of brain aging including the shift in synaptic plasticity, increased susceptibility to neural toxicity, and altered gene regulation.

Research directed at testing the effectiveness of treatments in ameliorating delaying/ ameliorating memory decline and preventing/reversing markers of brain aging includes behavioral treatments (exercise, environmental enrichment), diet (vitamin E, high fat, caloric restriction) and viral vector gene delivery (superoxide dismutase, estrogen receptor, growth factors).

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Dr. Abrams investigates memory and language processes in young and older adults, specifically the processes involved in retrieving words and the changes in these processes that occur with normal aging. Specific areas of interest include: (1) memory retrieval failures such as the tip-of-the-tongue (TOT) states, which are naturally-occurring retrieval failures that are characterized by a temporary inability to recall a known word; and (2) language errors such as the production of spelling errors and homophone substitution errors. One core question under study is: How do people spontaneously resolve their TOT states; how does the elusive word suddenly pop into mind, seemingly out of nowhere? Her research suggests that these resolutions are not accidental and instead are a direct result of encountering the sounds of the TOT word. Her work has identified more precisely that the initial syllable of the TOT word is the key; hearing or reading another word that shares the first syllable with the TOT word will resolve the TOT and allow the missing word to come to mind. Dr. Abrams has also discovered that grammatical class, specifically part of speech, plays a pivotal role in resolving TOT states: Only similar-sounding words that are a different part of speech from the TOT word are helpful. For example, if having a TOT for the word *rosary* (a noun), encountering an adjective like *robust* helps to resolve the TOT, whereas encountering another noun like *robot* does not. Furthermore, reaping the benefits of similar-sounding words on TOT resolution gets more difficult as we age. Adults in their upper 70s and 80s are less likely to resolve a TOT after encountering a similar-sounding word that is the same part of speech, relative to an unrelated word, suggesting an increased susceptibility for similar-sounding words to become fiercer competitors for retrieval. Dr. Abrams plans to continue studying the complex cognitive processes that underlie people's ability to produce language.

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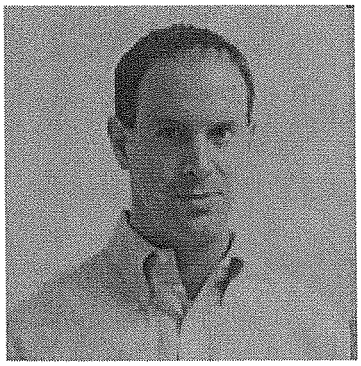

Dr. Stephen Anton is a Clinical/Health Psychologist with a strong interest in preventive medicine and healthy weight management. He is particularly interested in developing and testing the efficacy of lifestyle based (e.g., caloric restriction and exercise) and biological modalities (e.g., pharmaceuticals) for preventing and cognitive and physical decline associated with aging. Dr. Anton completed his B.A. in Psychology from Florida State University. He received his M.S. and Ph.D. in Clinical and Health Psychology from the University of Florida. Dr. Anton then completed a Postdoctoral Fellowship in Behavioral Medicine at the Pennington Biomedical Research Center , which is affiliated with Louisiana State University in Baton Rouge, LA. Dr. Anton has received many honors and awards. The University of Florida awarded him the J. Hills Miller Presidential Fellowship as a graduate student and he is a 2009 Outstanding Young Alumni Honoree for the College of Public Health and Health Professions. Dr. Anton is a member of the American Psychological Association, The Association for Advancement of Behavior Therapy (AABT), The Obesity Society and the Society of Behavioral Medicine. He has received research funding through the National Institute on Aging, the Pennington Biomedical Research Center, the Claude D. Pepper Older Americans Independence Center ,and the Evelyn F. and William L. McKnight Brain Institute among others.

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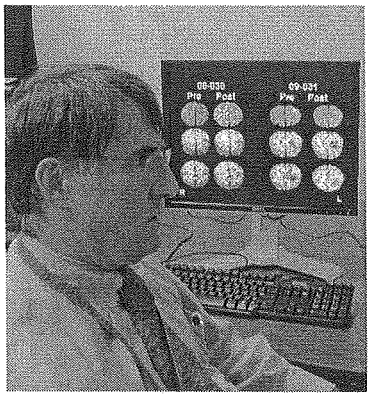

Dr. Crosson's interests are in understanding how brain systems support word retrieval and semantic memory and how neural plasticity makes relearning possible during rehabilitation. In addition to measures of behavior, word retrieval, and semantic memory, his laboratory relies heavily on functional and structural MRI. The current portfolio of projects in his laboratory includes studies of neural plasticity during aphasia rehabilitation, the integrity of the corticospinal tract and its role in upper extremity function after stroke, basal ganglia functions in language and semantic memory in 1991 Gulf War illness, and word retrieval models in Alzheimer's disease. A significant and related portion of his portfolio is dedicated to research on word retrieval, semantic memory, and episodic memory in aging. Two recent trends are prominent in the direction of his laboratory in aging research: (1) the literature on hemispheric asymmetry reduction in old adults (HAROLD) for tasks that are strongly lateralized in young adults and (2) the loss of interhemispheric inhibition during motor tasks in old adults. Recent discoveries from his laboratory include the applicability of the HAROLD phenomenon to frontal activity in simple word retrieval paradigms (both picture naming and category member generation), the intactness of the inferior temporal substrates for semantic memory in old adults, and dedifferentiation of the neural substrates of word retrieval in old-old vs. young-old adults. Current aging studies in the laboratory include: a study of interhemispheric inhibition during motor and word retrieval tasks in aerobically fit and sedentary old adults, the neural substrates of improved memory in neurologically normal adults taking Aricept vs placebo, and the role of relative task difficulty in recruitment of right frontal structures during word retrieval in young and old adults.

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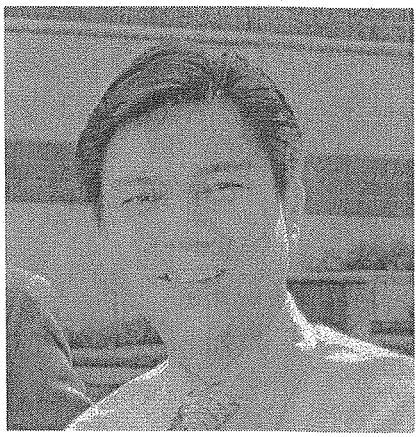

Hubert H. Fernandez, MD, is Associate Professor of Neurology, Director of Clinical Trials for Movement Disorders, Co-Director of the Movement Disorders Program, and Program Director of the Neurology Residency Training Program and Movement Disorders Fellowship Training Program, all at the University of Florida.
Dr. Fernandez is a Fellow of the American Academy of Neurology (also Executive Board Member of its Movement Disorders Section) and an active member of several professional societies, including the American Neurological Association, Movement Disorders Society (also a member of the Scientific Issues Committee; Chair of the Task Force on Psychosis Scales), and the Florida Society of Neurology (also an Executive Board Member and the President-elect). He is a member of several consortiums of academic clinical trial investigators: Parkinson Study Group (Co-Chair of the Functional Neurosurgical Working Group), Dystonia Study Group (also a member of the Executive Board), and Huntington Study Group. As a clinical trialist, Dr. Fernandez has a strong interest in designing and carrying out Phase II, III and IV clinical trials in Parkinson's disease and other movement disorders. He is particularly interested in the "non-motor" features of movement disorders such as dementia, psychosis, anxiety, depression, apathy, fatigue, etc. He has successfully led or participated in over 3 dozen single- and multi-center clinical trials in Parkinson's disease, dystonia, Huntington's disease and other movement disorders.

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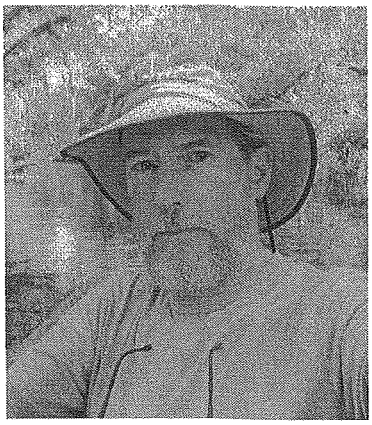

My laboratory is primarily interested in developing models of and therapeutics for dementing neuropathology associated with aging. We have developed and used adeno-associated viral vector technology to make preclinical gene delivery models of inherited and sporadic tauopathies, and inherited amyloidopathies, as well as age-related memory dysfunction related to the role of dephosphorylation in the MAPK pathway activated by neurotransmitter glutamate binding to metabotropic receptor subtype 5. We have also used the gene transfer approach to try to counteract tau, amyloid, and memory-related pathology by expressing degradative enzymes and neurotrophic factors. A pilot project is currently in progress to evaluate the potential for a microencapsulated formulation of the endogenous neuropeptide orexin to antagonize memory loss in aged, memory-impaired rats. Previous studies related to memory and aging include a comprehensive electrophysiological analysis of hippocampal synaptic function and plasticity across the lifespan of adult rats prior to the age when mnemonic dysfunction emerges. The laboratory is strongly focused on a variety of anatomical techniques including stereology and quantitative histometry. Behavioral assays include alternation, water maze, and avoidance learning and retention. Biochemical and molecular analyses of protein and gene expression, and intracellular signal transduction, complement anatomical, behavioral, and electrophysiological methods. Secondary interests of the lab include active collaboration in studies on septohippocampal development, stereotypy related to environmental impoverishment, the development of epilepsy, and histological validation of phenomena derived from magnetic resonance imaging techniques.

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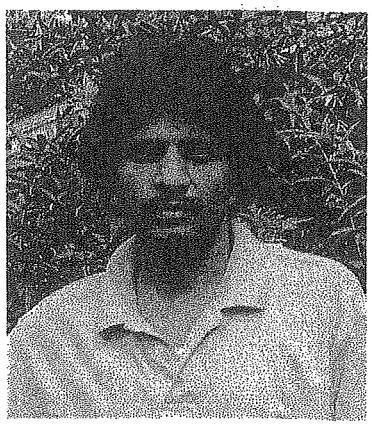

Dr. Kumar studies the role of Ca^{2+} dysregulation in altered synaptic function and its implication in age-related memory loss. Dysregulation of the Ca^{2+} homeostasis during aging contributes to various biological markers of brain aging including shift in synaptic plasticity and decreased neuronal excitability due to an augmented afterhyperpolarization (AHP) and spike frequency accommodation. Aging is associated with a shift in synaptic plasticity favoring long-term depression (LTD) over long-term potentiation (LTP) and Dr. Kumar has shown that the magnitude of the Ca^{2+} -dependent, K^+ mediated AHP plays a critical role in setting the threshold for induction of synaptic plasticity. Recently, Dr. Kumar has shown that Ca^{2+} release from intracellular Ca^{2+} stores and voltage gated Ca^{2+} channels contributes to the enhanced AHP and thus the threshold for LTP induction.

Dr. Kumar's research also involves delineating the impact of environmental enrichment and exercise on biological markers of brain aging and its effect on cognitive performance during senescence. Recently published results suggest that environmental enrichment reduced the augmented AHP in aged animals. In addition, Dr. Kumar's research also focused on unraveling the pharmacological and biochemical signaling pathways involved in chemically induced LTD by activation of group I metabotropic glutamate receptor and cholinergic receptor agonists. Findings published last year indicate that the magnitude of mGluR-induced LTD is enhanced in senescent animals and depends on activation of both mGluR 1 and 5 subtypes and requires Ca^{2+} from L-type Ca^{2+} channels.

Finally, Dr. Kumar also studies effects of estrogen on hippocampal function across the lifespan and his results indicate that estrogen rapidly increases neuronal excitability, decreases AHP, and augments the strength of synaptic transmission. Thus, taken together Dr. Kumar's research interest is to delineate the pharmacological, biochemical, and molecular mechanisms underlying biological markers of brain senescence, which underlie cognitive impairments associated with aging. Dr. Kumar earned his Master of Science from University of Lucknow and his Doctor of Philosophy in Pharmacology from Central Drug Research Institute, and is currently employed as a Research Assistant Professor and working in the laboratory of Dr. Thomas C. Foster at the University of Florida.

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Research in the Luesch lab lies at the interface of chemistry and biology and addresses multiple aspects of the drug discovery process ranging from assay development, identification and structure determination of bioactive small molecules, to studies toward the mechanism of action of small-molecule drug candidates and the discovery of novel putative drug targets. In our quest for small molecules with biomedical utility we mainly scrutinize natural products derived from marine cyanobacteria and eukaryotic algae. Active compounds are isolated using bioassay-guided fractionation and their structures determined using a combination of spectroscopic techniques. Subsequently, we use various genomic, proteomic and metabolomic profiling techniques to elucidate the mechanism of action of these compounds. We are also carrying out studies to disclose the function and action of genes/proteins that are putatively involved in cancer, aging, and neurodegeneration. Candidate genes are identified by high-throughput genome-wide screening. Validated genes are then subjected to molecular and biological characterization. The ultimate goal is to modulate gene or protein function with small molecules which could then be translated into valuable chemical biology tools or even novel drugs. Our recent focus has been on gene products that modulate oxidative stress levels through activation of the antioxidant response element (ARE). In humans, the ARE regulates the expression of a number of cytoprotective antioxidant enzymes and scavengers which contribute to the endogenous defense against oxidative stress. The activation of the ARE in the absence of general oxidative stress could provide a novel therapeutic approach for the treatment of various neurodegenerative diseases, stroke and aging. Dr. Luesch received his *Diplom* in Chemistry at the University of Siegen (Germany) in 1997. He attended the University of Hawaii at Manoa to study marine natural products chemistry and obtained his Ph.D. in Chemistry under the supervision of Prof. Richard E. Moore in 2002. He then undertook three years of postdoctoral studies as an Irving S. Sigal Fellow at The Scripps Research Institute in La Jolla under the guidance of Prof. Peter G. Schultz in the area of functional genomics. In 2005 he joined the faculty of the Department of Medicinal Chemistry at the University of Florida.

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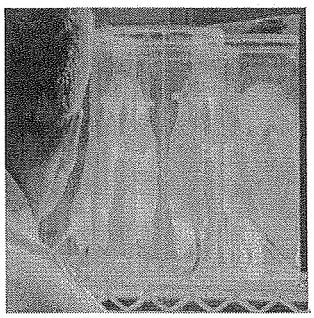

Dr. Mandel works with adeno-associated viruses and loads them with genetic information and substances like GDNF, looking for better treatments for Parkinson's, Huntington's and other disorders.

Dr. Ronald J. Mandel was born in Atlanta, Georgia. He attended Duke University where he obtained a BS in psychology. He then went to the University of Southern California where he studied the behavioral pharmacology of striatal dopamine receptors for his PhD work.

After his PhD, Dr. Mandel did his first post-doctoral fellowship with Leon Thal and Rusty Gage at UCSD where he worked on animal models of Alzheimer's disease. Dr. Mandel became interested in neural transplantation and took a second post-doctoral fellowship with Dr. Anders Björklund in Lund, Sweden, where he began studying Parkinson's and Huntington's disease. In 1991, Dr. Mandel took a job at the University of Illinois as an Assistant Professor.

Shortly thereafter, he took a position at the start-up biotechnology company Somatix Therapy Corporation to aid in developing a gene therapy for Parkinson's disease. He has continued this line of research since 1992, moving back to Sweden for one year in 1998 to complete an important part of this research. This brief return to Sweden was followed by taking an Associate Professorship in Neuroscience and in the Gene Therapy Center at the University of Florida in June of 1999 and he was promoted to full professor in 2005. In 2007, Dr. Mandel was appointed to the NIH Center for Scientific Review's Clinical Neuroplasticity and Neurotransmitters Study Section.

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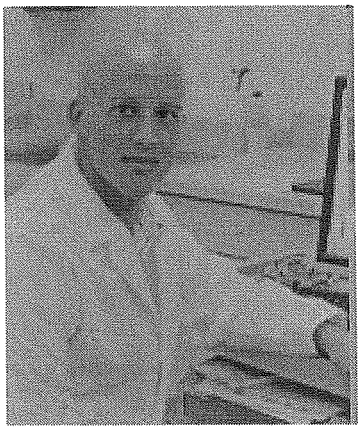

Dr. Manini's current research interests are focused on interventions that enhance cognitive performance in the elderly through the use of novel nutricueticals. He is partially supported by work that is testing a natural compound found in grapes and red wine that has previously been shown to extend lifespan in *S. erevisiae*, *C. elegans*, *Drosophila* and vertebrate fish. Resveratrol, a natural polyphenol found mainly in red wine and dark-skinned grape cultivars, has been shown to protect against cardiovascular diseases and cancers, as well as have anti-aging effects in numerous organisms. Resveratrol seems to work in SIRT1-dependent manner that is consistent with improved cellular function through anti-inflammatory effects. Additionally, pre-clinical models demonstrate that resveratrol supplementation improves memory performance and has significant neuroprotective effects. He is now implementing this compound in phase I clinical trial to determine whether resveratrol supplementation alters age-related memory function in older humans. This work contributes to overall research goals which are targeted toward enhancing quality of life among older adults.

Dr. Manini earned his B.S. from Ohio University in Athens, OH where he studied Biology, Exercise Science, and Biochemistry. He received his M.S. and Ph.D. as well as a Certificate of Advanced Studies in Gerontology from Syracuse University He completed a post-doctoral fellowship at the Laboratory of Epidemiology, Demography and Biometry at the National Institute on Aging at the National Institutes of Health in Bethesda, MD. Dr. Manini has received numerous awards and accolades. The Gerontological Society of America awarded him an Austin Bloch Post-Doctoral Fellow and named him a Clinical Medicine Research Award Honoree. He has contributed his expertise as a reviewer to numerous journals including The Journal of the American Medical Association, The Journals of Gerontology: Biological & Medical Sciences, The Journal of the American Geriatrics Society, and The British Medical Journal. Dr. Manini has received research funding from the National Center on Minority Health and Health Disparities, the National Institute on Aging, Claude D. Pepper Older American Independence Center, American College of Sports Medicine/F.M. Kirby Foundation, and from the Michael Pollack Memorial Grant Foundation. Rehabilitation.

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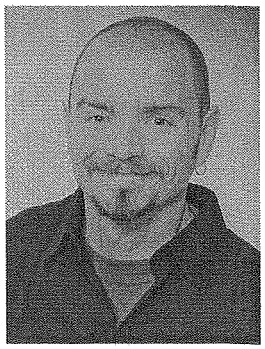

The central goal of Dr. Marshall's research is elucidate the connection between microglia (both intrinsic and bone marrow derived) and adult neurogenesis. His research involves the isolation and expansion of microglia from neurogenic regions of the brain and the subsequent transplantation of these cells back into the brains of aged mice. As a hematopoietic corollary to this work, bone marrow chimeras are generated using transgenic bone marrow from younger animals in order to ascertain the link between bone marrow derived microglia and age-related declines in neurogenesis. This work holds the potential to provide insights into determining the cellular cause for the well documented age-related declines in neurogenesis, as well as potential therapies for both cognitive decline and neurodegenerative disease states. Dr. Marshall is a postdoctoral fellow currently working under a NIH research training grant with the Center for the Neurobiology of Disease in the College of Pharmacy at the University of Florida.

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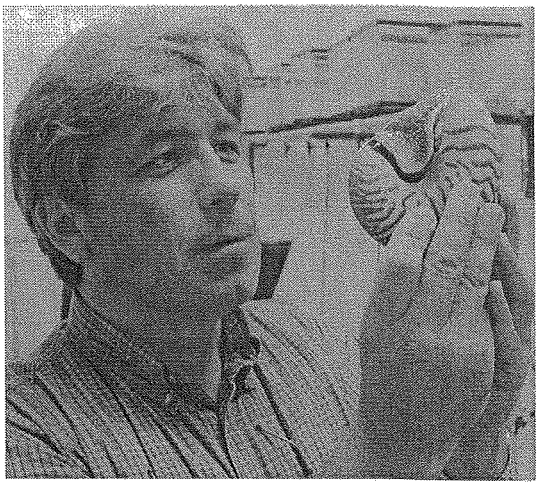

Dr. Moroz's major interest is in understanding the genomic bases of neuronal identity and plasticity in neural circuits including mechanisms underlying learning and memory.

The major questions are:
(1) why are individual neurons so different from each other,
(2) how do they maintain such precise connections between each other,
(3) how does this fixed wiring result in such enormous neuronal plasticity and
(4) how does this contribute to learning and memory mechanisms?

By taking advantage of relatively simpler nervous systems of invertebrate animals as models, we combine neuroscience, genomics, bioinformatics, evolutionary theory, zoology, molecular biology, microanalytical chemistry and nanoscience to understand how neurons operate, remember and learn.

Due to the tremendous difficulties in mapping single cells and processes in the mammalian brain, we study the giant neurons of the sea slug *Aplysia californica*, a well-established model organism for cellular and system neuroscience. Our objective is to investigate the activity of nearly all gene products in every neuron forming a simple memory-forming circuit during long-term plasticity and memory loss tests.

Recently, we have developed approaches to identify and quantify >99.9% of gene products from a single cell as well as to map epigenetic modifications of a cellular genome with single base resolution in this same cell. As a result, we are now investigating the genome-wide mechanisms of long-term plasticity in sensory, motor and interneurons of model memory circuits – a process that involves >10,000 distinct molecular players even within a single neuron. To understand the orchestrated activity of multiple gene regulatory networks we are developing computational and evolutionary approaches to model these processes.

The second direction in Dr. Moroz's lab is to understand the origin and evolution of neurons and nervous systems. It appears that neurons and complex brains have evolved several times independently in different animal lineages using similar molecular tool-kits and signal molecules.

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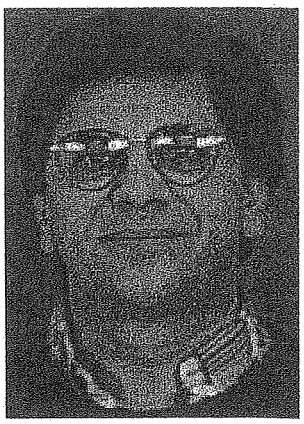

Nick Muzyczka was trained as a biochemist in DNA replication. As a postdoctoral fellow in Dan Nathans's laboratory, he developed the first SV40 vectors. When he moved to Florida, he then developed the first AAV vectors. For most of his career he has studied the basic molecular biology and biochemistry of AAV and worked out many of the technical issues related to the use of AAV for gene therapy. One of the technical problems that was solved was the modification of the coding sequence of the green fluorescent protein (GFP) gene so that it could be used in higher eukaryotes. This is now widely used by many laboratories. Muzyczka's lab also developed most of the production, purification and quantitation protocols currently in use today. In addition, Muzyczka's lab mapped the transcriptional signals of AAV, created the first genetic map of AAV, identified the components of the AAV origin for DNA replication, characterized the biochemical activities of the AAV non-structural Rep proteins, completely reconstructed AAV DNA replication in vitro with purified cellular components, and most recently, helped to crystallize and characterize mutants in the AAV capsid proteins. He is currently working on AAV capsid assembly and trafficking and trying to develop vectors that are specifically targeted to particular tissues or organs. Muzyczka has also collaborated with a number of investigators to bring rAAV vectors to clinical trials including the current trial for alpha-1-antitrypsin deficiency (a genetic pulmonary disorder) and the current trial for rpe65 deficiency (a form of congenital blindness). As part of a collaboration with Ron Mandel at the University of Florida to bring therapies for Parkinson Disease to the clinic, Muzyczka's lab has begun studying the function of alpha-synuclein, the major protein in Lewy bodies. His lab recently published work showing that the non-phosphorylated form of alpha-synuclein is non-toxic suggesting that Lewy bodies protect against Parkinson degeneration rather than promote it. In the learning and memory area, Muzyczka's lab first developed rAAV vectors that could quantitatively transduce the hippocampus. He then used a learning paradigm and microarrays to identify a number of genes in the hippocampal CA1 and dentate region that were likely to be involved in learning and memory. Most recently, he has tested three of the CA1 genes in the rat hippocampus by using rAAV vector gene transfer to overexpress these genes. All three genes (cycD1, pctk1, and tcf12) produced significant learning deficits in the radial arm water maze paradigm. Finally, Muzyczka's lab is also collaborating with Dave Morgan at USF to develop therapies for Alzheimer's Disease.

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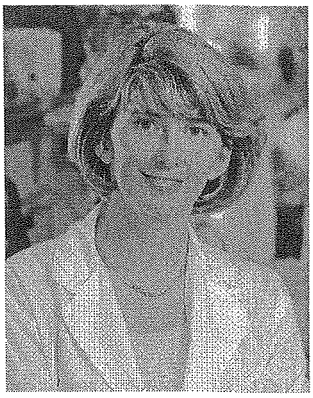

My laboratory investigates how protein homeostatic mechanisms, specifically the chaperone and autophagy-lysosomal pathways, are involved in the subcellular pathogenesis of neurodegenerative paradigms and in the age-related decline of neural function. While we examine the contribution of these basic mechanisms to disease processes, we are also exploring dietary and pharmacologic approaches to modulate these pathways. The main model system we use for our studies is Charcot-Marie-Tooth disease type 1A, an autosomal dominant demyelinating disorder of the peripheral nervous system. Using this paradigm, we are examining how cells respond to the accumulation of damaged and misfolded proteins and investigating approaches to prevent and reverse these events. Currently we are expanding these studies to rodent models of aging. Along with our investigations concerning age-, toxin- and genetically-linked alterations in the nervous system, we are interested in understanding mechanisms that mediate the differentiation and interactions of neurons and glia. A recently discovered mechanism for differential gene expression in related cells is the utilization of microRNAs. Ongoing experiments are aimed at determining which specific miRNAs regulate the expression of key glial proteins at specific stages of neural development.

Dr. Notterpek received a B.A. in Anatomy-Physiology from the University of California at Berkeley. She obtained her Ph.D. in Neuroscience at the University of California at Los Angeles working with Dr. Leonard H. Rome. Her postdoctoral training was under the guidance of Dr. Eric Shooter at Stanford University. Currently, Dr. Notterpek is Associate Professor and Chair in the Department of Neuroscience at the McKnight Brain Institute of the University of Florida. She is recipient of the 2004 Jordi Folch-Pi Memorial Award, from the American Society of Neurochemistry, to a young scientist for research excellence. She has authored and coauthored over forty peer-reviewed publications. She is actively involved in the educational and research missions of the College of Medicine at the University of Florida. Her research efforts are being supported by the NIH, the National Muscular Dystrophy Association and the National Multiple Sclerosis Society.

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Dr. Ormerod's research seeks to understand whether and how stem cells could repair the injured or diseased brain. Ground-breaking work by Sam Weiss' and Elizabeth Gould's groups in the 1990's showed respectively that neural stem/progenitor cells resided in the adult CNS and actually generated neurons each day through life in the hippocampal dentate gyri of mice and men alike. The discovery of CNS neural progenitor cells and the re-discovery of adult hippocampal neurogenesis was exciting for several reasons. First, they suggested that the CNS harbored regenerative potential that could be mobilized to repair diseased or damaged brain circuits. Second, they suggested a novel and dramatic form of plasticity in a structure implicated in forms of learning and memory; the hippocampus. Third, they showed that if the environment could be made permissable, multiple stem cell sources (hESCs, IPCs, etc) could be used to repair diseased or damaged circuits; ongoing hippocampal neurogenesis could model how tranplantable cells might behave *in situ*. The Ormerod Laboratory specifically focuses upon understanding how neuroinflammation (which accompanies all neurodegenerative disease) impacts hippocampal neurogenesis (*in vivo* work) and neural progenitor cell behavior (*in vitro* work). We have shown that neuroinflammation ablates hippocampal neurogenesis and produces a latent memory impairment. Both problems can be reversed with the appropriate non-steroidal anti-inflammatory drug (PPARy activators, but not COX-2 inhibitors). We are currently investigating what component of the neuroinflammatory response impacts neural stem cell behavior in rats, transgenic mice, and in co-culture systems. We are interested in understanding whether the hippocampal response to inflammatory stimuli is unique relative to other brain tissue. Along with Dr. Tom Foster, we are investigating whether age-related changes in cognition can be predicted by systemic and/or central biomarkers and whether altered hippocampal neurogenesis may underlie these changes.

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Heather Ross is a Research Assistant Professor in the Department of Physical Therapy at the University of Florida. Dr. Ross earned a Ph.D. in Anatomy and Neurobiology from Virginia Commonwealth University in 2006. She then worked as a postdoctoral fellow for Dr. Eric Laywell in the University of Florida's Department of Anatomy and Cell Biology. There, she focused on the role of thymidine analogs in neural stem cells and in cancer cells. Dr. Ross's research interests are centered on the modulation of neural stem cells and how that ultimately affects downstream function. Current studies involve participation in three projects: 1) DNA and epigenetic alterations in neural stem cells and cancer cells following thymidine analog uptake; and how this may respectively mimic components of aging as well as target primary/recurrent brain tumor. 2) The age-related and instructive role of microglia on persistent neurogenesis. 3) The combinatorial approach of neural stem cell therapies and rehabilitation strategies following neural insult. The long-term goal of these studies is to further the basic understanding of mechanisms behind the modulation of neural stem cells, and to use this information to optimize the translational benefit of neural cell replacement therapies and subsequent patient outcomes.

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The goal of my research program is to understand how mutations in genes expressed in the fetal brain lead to abnormal development and dysfunction of the cerebral cortex. Development of the cortex is a highly orchestrated process, the disruption of which often leads to mental retardation, seizures, autism, and abnormalities in learning and memory. Detailed examination of the developing brains of animals carrying theses mutations will allow us to identify the specific developmental events affected by these mutations, information that could lead to development of therapeutic strategies for these devastating neural diseases.

Our current research is focused on investigations of the MAPK signaling pathway, and on the development and function of neuronal primary cilia. The MAPK pathway plays a critical role in coordinating the response of cells to various extracellular stimuli. Disruptions of this pathway often lead to abnormal neuronal migration and differentiation in the developing brain. Neuronal cilia have, until recently, received little attention. Mutations in cilia genes have been linked to a number of neurological disorders in humans. Through collaborative efforts, we identified a new gene, *stumpy*, that encodes a protein that plays an important role in cilia growth. Mice lacking Stumpy fail to develop neuronal cilia and exhibit a variety of developmental abnormalities in the cerebral cortex. To investigate MAPK signaling and neuronal cilia we analyze developing normal and mutant brain using biochemical, molecular, cell culture, histological, and *in vivo* genetic assays.

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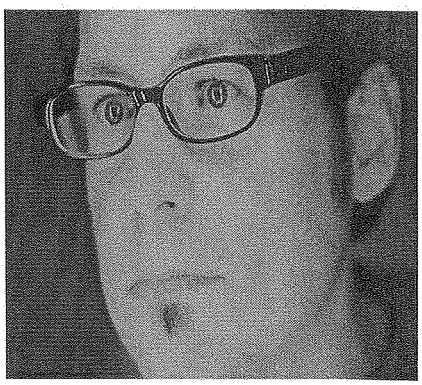

The main focus of Dr. Siebzehnrubl's research is the characterization of stem cells of the adult human brain, in particular in the context of neurodegenerative disorders of the striatum, i.e. Parkinson's and Huntington's disease. A main goal is the development of an experimental, adult stem cell-based therapy for Parkinson's disease. Employing genetically modified adult human neuroprogenitors that release survival factors for dopaminergic neurons, this therapy is aimed at preserving and restoring dopaminergic innervation of the striatum. This program involves stem cell grafting in rodent models of Parkinson's disease, as well as behavioral testing and basic neuroscience research techniques.

Another area of interest targets adult subventricular zone stem cells in Huntington's disease. Functional anomalies of stem cell migration and differentiation are analyzed in a transgenic animal model of Huntington's disease. Using organotypic slice cultures as a platform for time-lapse imaging as well as fate mapping, this work aims to provide a basis for the search of stem cell-targeting therapeutic compounds.

A recent study currently being submitted unveiled a direct relation between memory capacity and neuronal differentiation of multipotent hippocampal progenitor cells in epilepsy patients. This indicates neurogenesis-dependent memory function in human subjects.

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Ralph L. Sacco, MD, MS, FAHA, FAAN

Ralph L. Sacco, MD, MS, is the Chairman of Neurology, Olemberg Family Chair in Neurological Disorders, Miller Professor of Neurology, Epidemiology, and Human Genetics at the Miller School of Medicine, University of Miami and Chief of the Neurology Service at Jackson Memorial Hospital. He was the former Professor of Neurology and Director of the Stroke and Critical Care Division at the Neurological Institute of Columbia University College of Physicians and Surgeons, the Mailman School of Public Health, and the Sergievsky Center.

Dr. Sacco graduated from Cornell University with distinction, received his medical degree cum laude from Boston University School of Medicine in Massachusetts, and a master's degree in epidemiology from Columbia University, School of Public Health. Dr. Sacco completed a residency in neurology at Presbyterian Hospital of the City of New York. He completed his postdoctoral training in stroke and Epidemiology at Columbia under a NINDS-funded neuroepidemiology training grant.

Dr. Sacco's clinical research activities began in 1980 when he participated in the Framingham Heart Study. Since 1990, he has been the Principal Investigator of the Northern Manhattan Study an NIH-funded community-based, epidemiologic study designed to determine stroke incidence, risk factors, and prognosis in an elderly, multi-ethnic, urban population living in northern Manhattan in New York City. This study now includes a separate NINDS-funded project, the Northern Manhattan Family Study, to evaluate potential genetic determinants of stroke risk factors.

Dr. Sacco was also the founding principal investigator of the NY Columbia Collaborative Specialized Program in Translational Research in Acute Stroke. He is also co-investigator of six other NINDS grants. He has been involved in the design and conduct of multiple randomized trials including the co-principal investigator of the Warfarin Aspirin Recurrent Stroke Study, the principal investigator of the Glycine Antagonist in Neuroprotection Trial, and the current co-chair of the international PRoFESS Study (Prevention Regimen for Effectively avoiding Second Strokes). He serves on the Data Safety and Monitoring Boards of a number of NIH and pharmaceutical-sponsored clinical trials. In addition, Dr. Sacco is on the editorial board of *Stroke, Neuroepidemiology*, and *Nature Clinical Practice Neurology*. He has published extensively in the areas of stroke prevention, treatment, risk factors and stroke recurrence, with more than 475 original articles, case reports, book chapters, abstracts and communications to his credit. He has been a principal author on numerous evidence-based guidelines from the AHA and ACCP. He has helped train numerous fellows in stroke and epidemiology. He has been awarded the 2006 Feinberg Award for Excellence in Clinical Stroke and the 2007 Chairman's Award from the American Heart Association. In 2008, he received the Javits Award in Neuroscience and was inducted into the American Association of Physicians.

Dr. Sacco is a fellow of the Stroke and Epidemiology Councils of the American Heart Association, a Fellow of the American Academy of Neurology, a member of the American Neurological Association, past chair of the Clinical Research Committee of the American Academy of Neurology, and on the Medical Advisory Board of the Hazel K. Goddess Fund for Stroke Research in Women. He is a past member of the Epidemiology and Disease Control-3 NIH Study Section, NINDS Neuroscience Training Review Committee, and FDA Advisory Panel for Central and Peripheral Nervous System Drugs. He is a former member of the Board of Directors for the American Heart Association, and a current member of the Board for the American Academy of Neurology and past president of the New York City AHA Board. He is a past member of the Stroke Prevention Advisory Panel of the National Stroke Association and past chair of the Stroke Advisory Committee of the American Stroke Association. Most recently, and not yet formally announced, Dr. Sacco has been accepted the nomination to serve as President-elect of the American Heart Association for the 2009-2010 term that begins in June, and will serve as President of the American Heart Association for the 2010-2011 term.

Susan Halloran Blanton, Ph.D.
Associate Professor of Human Genetics
Associate Director of Communications and Compliance
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Dr. Blanton's primary research has focused on the mapping of Mendelian and complex diseases. Stroke and the underlying genetics of risk factors, deafness, retinal diseases, skeletal dysplasias, cleft lip/palate, and club foot are among the diseases which she currently studies. She has also been involved in developing and implementing genetic education materials for Federal and appellate level judges and science writers in an ELSI sponsored project. Her current research also involves determining the level of genetic knowledge and attitudes towards genetic testing among the deaf as well as developing methods for integrating genetics into the private practice setting. Dr. Blanton is Associate Director of Communications and Compliance at the MIHG, Associate Professor of the Dr. John T. Macdonald Foundation Department of Human Genetics, and Chief of the Division of Genomic Medicine.

Richard S. Isaacson, MD
Assistant Professor of Neurology and Medicine
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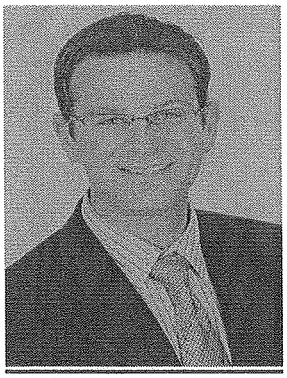
Director, Neurology Residency Training Program
University of Miami, Miller School of Medicine



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A graduate of the accelerated 6-year B.A./M.D. program at the University of Missouri at Kansas City School of Medicine, Dr. Isaacson currently serves as the Associate Chair for Education and Director of the Neurology Residency Program in the Department of Neurology at the University of Miami Miller School of Medicine. He completed his residency in Neurology at Beth Israel Deaconess Medical Center/Harvard Medical School, and his medical internship at Mount Sinai Medical Center in Miami Beach, FL. Prior to joining the University of Miami, he served as Director of the Research Unit in Medical Education and Associate Medical Director of the Wien Center for Alzheimer's disease and Memory Disorders at Mount Sinai.

Dr. Isaacson chairs the American Academy of Neurology (AAN) Undergraduate Education Subcommittee working group in dementia, which is responsible for making recommendations of what is taught to medical students around the country. He is the recipient of the AAN Education Research Grant for his project "Evaluating the effectiveness of *Continuum*: Dementia as a teaching tool for medical students" and has recently completed a study on "Evaluating the effectiveness of a Cognitive Aging curriculum for medical students, Internal Medicine and Neurology residents". He is funded by National Institutes of Health Clinical Research LRP for his project entitled "Genetic and Environmental Determinants of White Matter Hyperintensities and Vascular Cognitive Impairment", and is the author of numerous abstracts and publications. His research in neurology and medical education has been presented at scientific meetings nationally and internationally.

Bonnie E. Levin, Ph.D.
Director, Division of Neuropsychology
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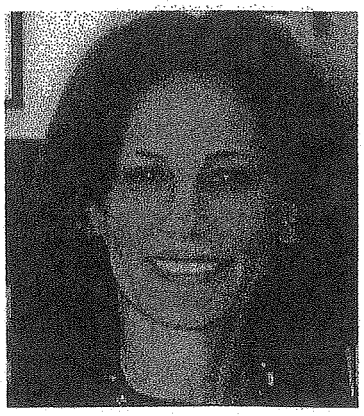

Dr. Levin is a neuropsychologist whose research examines neurocognitive and affective changes associated with neurodegenerative disease and the normative again process. Her work examines the inter-relationship between behavioral and motor symptoms in Parkinson's disease and the neural circuitry underlying memory and age related cognitive decline. Her current work is aimed to advance our understanding of frontal striatal circuit function in cognition and to generate data that will improve our knowledge of key clinical parameters associated with differential rates of cognitive decline. Current projects include: imaging and clinical correlates of white matter changes associated with the aging process and structural and metabolic markers underlying different symptom profiles in neurodegenerative disease. Dr. Levin is an Associate Professor of Neurology and Psychology and is the Director of the Division of Neuropsychology within the Department of Neurology at the University of Miami Miller School of Medicine.

Fatta B. Nahab, M.D.
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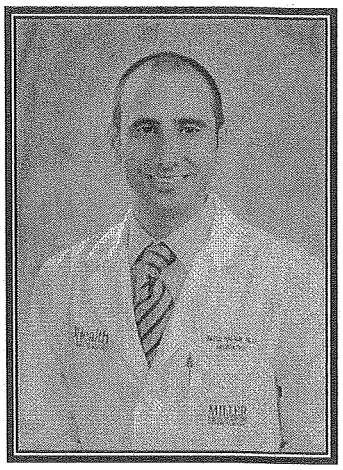
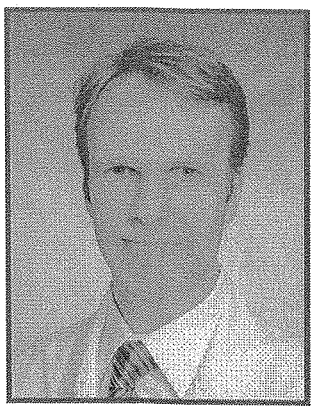


The main focus of Dr. Nahab's research focuses on the development of novel functional neuroimaging methodologies to characterize the neural correlates of tremor disorders such as Parkinson disease (PD) and Essential tremor (ET). Dr. Nahab has also conducted phase I/II clinical trials of novel agents to treat ET, for which he was awarded co-inventor status on two patents. Dr. Nahab joined the department of Neurology at the University of Miami in 2008 to help expand functional neuroimaging, both within the department and across the institution. Ongoing research continues to explore the neural mechanisms underlying tremors. In addition, Dr. Nahab maintains a weekly clinical schedule at the University of Miami Parkinson's Disease Center of Excellence.



Clinton B. Wright, M.D., M.S.
Scientific Director
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Dr. Wright came to the Miller School of Medicine at the University of Miami in July 2008 from the College of Physicians and Surgeons of Columbia University. As Scientific Director of the Evelyn F. McKnight Center for Age Related Memory Loss, Dr. Wright is developing a translational research program that examines normal cognitive aging and its distinction from pathological states, with a special emphasis on the role of subclinical cerebrovascular disease. Dr. Wright is directing the Division of Cognitive Disorders and establishing a clinical arm to enhance these efforts.

Dr. Wright graduated from George Washington with honors in psychology, and received his medical degree from the College of Physicians and Surgeons of Columbia University. He completed residency training in neurology at the Neurological Institute of New York and the Columbia University Medical Center. Following residency, Dr. Wright completed a vascular neurology fellowship as well as a Master of Science degree in epidemiology from the Mailman School of Public Health under an NINDS-funded neuroepidemiology training grant.

Dr. Wright's is currently funded by the American Heart Association and the National Institutes of Neurological Disorders and Stroke to examine race-ethnic disparities and the effects of vascular risk factors on brain structure and function, with an emphasis on early cognitive changes. He is Chair of the Neuroimaging and Cognitive studies within the Northern Manhattan Study, an urban multi-ethnic population-based cohort study in New York. Recent studies include the determinants of subclinical cerebral infarction as measured by magnetic resonance imaging and the effects of ischemic white matter damage as well as subclinical infarction on cognitive functions such as psychomotor speed and cognitive flexibility. As part of the Columbia University Specialized Programs On Translational Research In Acute Stroke (SPOTRIAS) program, Dr. Wright developed a cognitive assessment battery that has been administered to several hundred stroke patients to examine the acute effects of stroke on cognition and consequences for getting appropriate medical care at the time of second stroke.